A Nested Case Control study to evaluate the association between Dyslipidemia and Hypertensive disorder of pregnancy in a tertiary care hospital in South India.

A dissertation submitted in partial fulfilment of MS Obstetrics and Gynaecology (Branch VI) examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2019

DECLARATION

I declare that the dissertation entitled **"A Nested Case Control study to evaluate the association between Dyslipidemia and Hypertensive disorder of pregnancy in a tertiary care hospital in South India"** is my original work done in partial fulfilment of the requirement for MS Obstetrics and Gynaecology (Branch VI) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2019.

Dr. Sarin Varghese
Post graduate student (MS Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology
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Vellore -632004

CERTIFICATE

This is to certify that the dissertation entitled **“”** **A Nested Case Control study to evaluate the association between Dyslipidemia and Hypertensive disorder of pregnancy in a tertiary care hospital in South India”** is the bonafide original work of Dr. Sarin Varghese submitted in partial fulfilment of the requirement for MS Obstetrics and Gynaecology (Branch VI) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2019

Guide:

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Professor and Head

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Principal
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Professor
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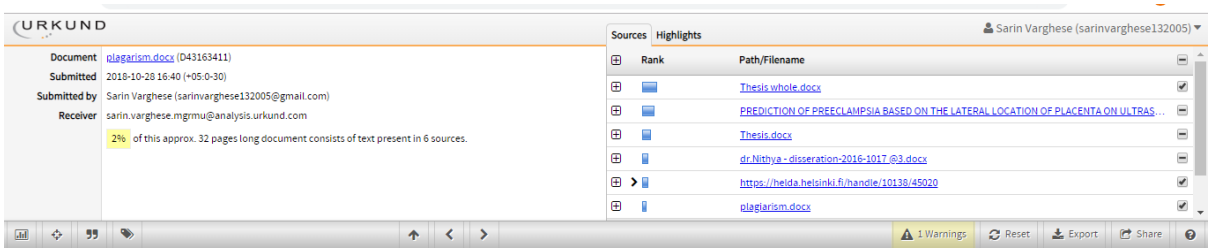

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Association of Dyslipidemia and Hypertensive disorders in pregnancy in a tertiary care hospital in South India- A Nested case control study.
Dr. Sarin Varghese, Employment Number: 21099, Junior resident/ Department of Obstetrics and Gynecology/ OG3, Dr. Anne Regi, Emp No: 11190 OG3, Dr. Anuja Abraham, Emp No: 31916 OG3, Dr. S. Vanitha, biochemistry, Hepsy V S, Biostatistics.

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Dear Dr. Sarin Varghese,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

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Dear Dr. Sarin Varghese,

The Institutional Review Board **(Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Association of Dyslipidemia and Hypertensive disorders in pregnancy in a tertiary care hospital in South India- A Nested case control study" on September 04th 2017.

The Committee reviewed the following documents:

1. IRB Application Format
2. Patient Information Sheet and Consent Form
3. Cvs of Drs. Hepsy, Sarin Varghese, Anuja, Annie Reji, Ms. Vinitha
4. No. of documents 1- 3.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on September 04th 2017 in the Jacob Chandy Hall, Paul Brand Building, Christian Medical College, Vellore 632 004.

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Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
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We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Association of Dyslipidemia and Hypertensive disorders in pregnancy in a tertiary care hospital in South India- A Nested case control study" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 50,000/- INR (Rupees Fifty Thousand Only) will be granted for 12 months.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
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Table of Contents

ABSTRACT

Introduction

Hypertensive disorders of pregnancy are an elusive group of diseases with varied manifestation and multifactorial etiopathologies. One of the leading hypothesis is that endothelial dysfunction in the maternal circulation is the most imperative factor which leads to development of hypertensive disorder of pregnancy. Abnormal lipid profile is shown to have a positive correlation with endothelial dysfunction. Even though pregnancy is a hyperlipidaemic state, the dyslipidaemia is more pronounced in women who develop hypertensive disorders of pregnancy than their normotensive counterparts. In this study, we tried to assess whether first trimester dyslipidemia has a significant correlation with hypertensive disorders of pregnancy which in turn in future be used as predictive marker for the same.

Aims and objectives

Aim: To determine if dyslipidemia is a predisposing factor for development of hypertensive disorders of pregnancy.

Objectives:

1.To assess if dyslipidemia diagnosed early in pregnancy will predispose to hypertensive disorders of pregnancy.

2. To assess whether severity of dyslipidemia correlates with severity of hypertensive disorders.

Materials and methods

Women presenting to the antenatal OPD of Obstetrics department, Christian Medical College with singleton pregnancy with GA less than 16 weeks were approached. Patients were recruited after consent and morning fasting lipid profile was collected. The collected samples were centrifuged and the serum was stored in Biochemistry lab. Patients were followed up till after the delivery.

Results

First trimester Hypercholesterolemia is significantly correlated with developing hypertensive disorders in later pregnancy, but this was not significant when gestational hypertension was compared with Preeclampsia. There was moderate correlation between first trimester hypertriglyceridemia and hypertensive disorder of pregnancy but there was no such association with increasing severity of hypertension in pregnancy. First trimester HDL and LDL levels do not show any significant correlation with hypertensive disorders of pregnancy.

Conclusion

Hypercholesterolemia and hypertriglyceridemia in first trimester are related to development of hypertensive disorders, but a much larger study is needed to predict if it can be used as predictive marker for same.

Keywords

Hypertensive disorders of pregnancy, Dyslipidemia, Preeclampsia

INTRODUCTION

Hypertensive disorders of pregnancy constitute an elusive and challenging group of pregnancy disorders that leads to considerable burden of illness in both industrialised and non-industrialised countries. Recent WHO survey has indicated that there is an alarming rise in the incidence of hypertension in pregnancy. It is the single largest direct cause of maternal mortality in industrialised countries (1). Hypertension complicates 3-10 % of all pregnancies worldwide varying in different countries, of which 4-8% are complicated by preeclampsia (2). There has been a gradual increase in the incidence of chronic hypertension, Gestational hypertension and Preeclampsia in the past decades, which has been attributed to changes in maternal characteristics such as maternal age, obesity and use of assisted reproductive techniques(3).

The multifactorial determinants of pre-eclampsia which encompasses genetic, familial, behavioural, epidemiological and environmental factors has been a real enigma. The recent interest in preeclampsia is due to the now established fact that having preeclampsia in pregnancy is not only a peripartum complication but also predisposes the mother to cardiovascular complications later in life. Even children born to mother with preeclampsia are more likely to suffer from metabolic syndrome, cardiovascular disorders and hypertensives disorders at an early age (4).

Considering the disease burden of hypertensive disorder of pregnancy, there have been different theories and research to determine the probable pathophysiology as to why some women are more prone to develop hypertensive disorders of pregnancy and others are not. Many biochemical and biophysical markers have been investigated

based on the pathophysiological observations that have been noted in cases of preeclampsia, such as placental dysfunction, generalised inflammatory response, endothelial dysfunction and activation of coagulation system(5).

Abnormal lipid profiles have a strong positive correlation with endothelial dysfunction. Normal pregnancies have shown physiological hyperlipidemia which is under hormonal control (6,7). Women with preeclampsia have more pronounced dyslipidemia than in women without preeclampsia (8,9). Evidence from few available prospective cohort studies suggest that women destined to develop the disorder are more likely to have elevated plasma triglycerides and decreased HDL cholesterol concentrations compared with their normotensive counterparts(8,10–12).

Majority of these studies have corelated deranged lipid profiles with hypertensive disorders, but most of these studies have been limited by the fact that the blood samples were collected after a diagnosis of preeclampsia is made. Hence such studies were inconclusive as the confounding factors were not adjusted (8,10,11). Enquobahrie et al. did a prospective study on a cohort of women who received prenatal care before 16 weeks. They examined various concentration of plasma lipids and lipoproteins measured in early pregnancy and compared these with their normotensive counterparts and found that early pregnancy dyslipidemia was associated with an increased risk of preeclampsia(13). We attempt to determine with this study whether doing a single measurement of serum lipid profile in early pregnancy will be of predictive value in identifying women at risk of developing hypertensive disorders of pregnancy.

AIMS AND OBJECTIVES

Aim: To determine if dyslipidemia is a predisposing factor for development of hypertensive disorders of pregnancy.

Objectives:

1. To assess if dyslipidemia, diagnosed early in pregnancy will predispose to hypertensive disorders of pregnancy.

2. To assess whether severity of dyslipidemia correlates with severity of hypertensive disorders.

REVIEW OF LITERATURE

Hypertensive disorders of pregnancy complicates 3-10 % all pregnancies worldwide and preeclampsia about 2-4%.

Classification of hypertensive disorders of pregnancy by ACOG 2013

1) Chronic hypertension

- Blood pressure ≥140/90 mmHg before pregnancy and at <20 weeks of gestation, or diagnosed for the first time during pregnancy and does not resolve postpartum.

2) Gestational hypertension

- New-onset blood pressure ≥140/90 mmHg detected at ≥20 weeks gestation without proteinuria.
- Pre-eclampsia does not develop and blood pressure returns to normal by 12 weeks postpartum.

3) Pre-eclampsia and eclampsia

- Blood pressure ≥140/90 mmHg on two occasions at least 4 h apart or ≥160/110 mmHg within a shorter interval (minutes), at ≥20 weeks of gestation, in women with previously normal blood pressure and proteinuria*.

- In the absence of proteinuria, new-onset hypertension plus new onset of any of the following features: serum creatinine concentrations >97 µmol/l or doubling of serum creatinine concentration in the absence of other renal disease; elevation of liver transaminases to twice normal concentration; pulmonary oedema; and cerebral or visual symptoms
- Eclampsia: seizures in women with pre-eclampsia that cannot be attributed to other causes
- Atypical form of preeclampsia presents with systemic symptoms, abnormal haematological tests or elevated liver enzymes without proteinuria.

4) Pre-eclampsia superimposed on chronic hypertension

- Women with hypertension (at <20 weeks gestation) and new-onset proteinuria*
- In women with hypertension and proteinuria* (at <20 weeks gestation), development of any of the following features: sudden increase in proteinuria;* sudden increase in blood pressure in women whose hypertension was previously well controlled; thrombocytopenia (platelet count <100,000 per mm^3); and elevated liver transaminase levels.

*Defined as urinary protein excretion ≥300 mg/24 h, a total protein:creatinine ratio ≥30 mg/mmol (or ≥0.3 when both are measured in mg/dl) or a dipstick reading of ≥1+ (only if other quantitative methods are not available).

(14)

Classification of pre-eclampsia

1) Early pre-eclampsia (<34 weeks*)

- Uncommon (prevalence 0.38% or 12% of all pre-eclampsia)
- Associated with extensive villous and vascular lesions of the placenta

2) Late pre-eclampsia (≥34 weeks*)

- Minimal placental lesions
- Maternal factors (such as metabolic syndrome and hypertension) have important roles
- Most cases of eclampsia and maternal death occur in late disease.

*Gestational age at diagnosis or delivery(15)

The recent interest in preeclampsia is due to the now established fact that having preeclampsia in pregnancy is not only a peripartum complication but also predisposes the mother to cardiovascular complications later in life. Even children born to mother with preeclampsia are more likely to suffer from metabolic syndrome, cardiovascular disorders and hypertensives disorders at an early age (4).

Long term consequences:

Maternal consequences

There have been many genetic, environmental and behavioural factors implicated to be involved in pathophysiology (16). Epidemiological studies have identified various characteristics which increases the risk of developing preeclampsia in pregnancy. These studies have identified nulliparity, primigravida, obesity, prior history of gestational hypertension, assisted reproductive techniques, extremes of maternal age, family history, short sperm exposure as risk factors for developing preeclampsia.(17). Many of the risk factors which cause metabolic syndrome are also the risk factors which cause preeclampsia(18). A study done in 2005 showed that mortality due to premature cardiovascular disease, cerebrovascular disease, peripheral artery disease was twice high in women with history of preeclampsia and the severity of preeclampsia had significant relation to metabolic syndrome (19). Women with polycystic ovarian syndrome are more likely to have adverse pregnancy outcome even when they are not obese as they have more insulin resistance leading to metabolic syndrome and hypertensive diseases of pregnancy(20). The health, aging and body composition study found that Odds ratio of developing Cardiovascular disease was 3.31 for women who delivered infants that were both preterm and <2500gm compared with women who had normal weight infants at term (21). A positive obstetrical history for preeclampsia doubles the risk for Cardiovascular diseases in mother (22).

Foetal consequences

Children born to obese mothers have been shown to have increased mortality when compared to children born to mothers with normal BMI (23). Even long term studies have shown that adults who were born to mothers with high BMI and Increased waist circumference have increased blood pressure, triglyceride levels and insulin resistance (24). Such children also require more hospital admissions from all cardiovascular complication combined. The observed relation was independent of other combined confounders such as maternal social class, maternal parity, current age and sex of the offspring (23). The adverse in utero conditions during developmental period leads to lifelong changes in body composition and physiology with resultant adverse effect in adulthood (25). Recently fatty streaks have been found in aortas of foetuses aborted at 6 months in mothers with Hypercholesterolemia.(9) Studies have also identified aortic atherosclerosis during autopsy of deceased children with normal cholesterol levels born to mothers with hypercholesterolemia(25). Atherosclerosis was among the first condition for which the developmental programming was described. Metabolic, environmental genetics, parental lifestyle are important pre-pregnancy factors that contribute to foetal programming. At the cellular level, adaptations occur by DNA methylation and chromatin modification maybe responsible for epigenetic programming leading to increased atherosclerotic susceptibility (27). The interface between the genome and environment is responsible for epigenetic phenomena. The influence of environment can influence epigenetic information which is superimposed on DNA, which have long term consequences for transcription of specific segment of

genome leading to atherosclerotic susceptibility(28). For instance Maternal hypercholesterolemia in Apolipoprotein E deficient mice leads to activation of gene involved in cholesterol synthesis and Low density lipoprotein receptor activity in adulthood of the mice(28,29). Even other animal studies have shown that the genes involved in immune pathways and fatty acid metabolism gets upregulated in mothers with hypercholesterolemia (30). Hence it is clear that adverse in utero condition in mother is responsible for foetal genetic programming at cellular level making them susceptible to various adverse effects.

Further research is needed to unravel how exactly maternal hypercholesterolemia influences these genetic mechanisms.

Etiopathogenesis

Even though hypertensive disorders of pregnancy are a leading cause of maternal and foetal mortality and morbidity, the pathophysiology of it is not entirely understood(14). The pathology of development of hypertension in pregnancy is different from the hypertension caused prior to conception.

The theory concerning the aetiology and pathogenesis of preeclampsia must account for the observation that gestational hypertensive disorders are more likely to develop in women with following characteristics-

- Are exposed to chorionic villi for the first time in life
- Are exposed to a superabundance of chorionic villi, as with twins or hydatiform mole.
- Have pre-existing conditions of endothelial cell activation or inflammation such as diabetes or renal or cardiovascular disease.
- Are genetically susceptible to hypertension developing during pregnancy.

The foetus is not a requisite for preeclampsia to develop but the presence of chorionic villi is essential(31)

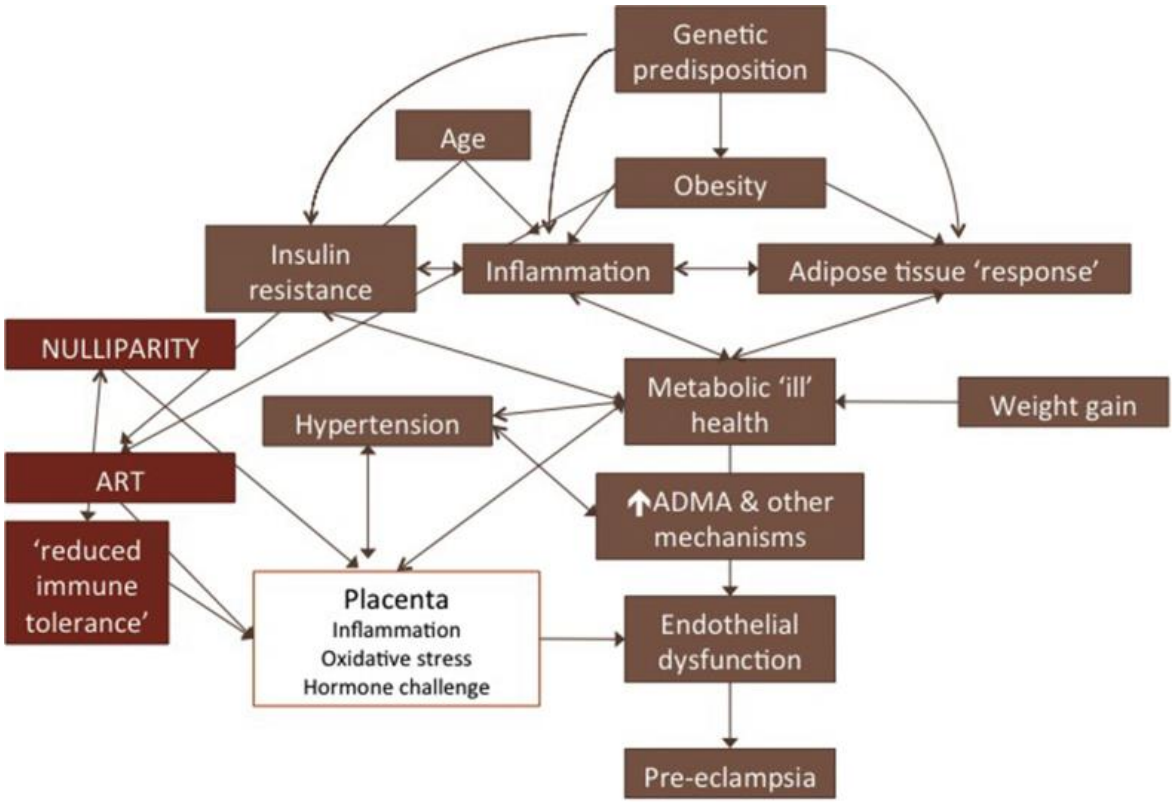


Figure 1: Metabolic precursors for preeclampsia(32)

Pathophysiology of Preeclampsia

The essential hypothesis central to our understanding of pre-eclampsia is that the disorder is a consequence of ischaemia of the placenta, which in turn releases factors

into the maternal circulation that can induce the clinical manifestations of the disease. This concept arose from observations that placental infarctions are common in patients with eclampsia.

Important mechanisms involved include:

1. Placental implantation and abnormal trophoblastic invasion of uterine vessels.
2. Maternal maladaptation to cardiovascular and or inflammatory changes of pregnancy.
3. Placental hypoperfusion and hypoxia.
4. Immunological maladaptive tolerance between maternal, placental and foetal tissues.
5. Genetic factors including inherited predisposing genes and epigenetic influences.(31)

1. Abnormal trophoblastic invasion

Human pregnancy is characterized by deep placentation, trophoblastic cells not only invade the decidua but also more than one third of myometrium.(33,34) As invasive trophoblasts transform the spiral arteries some researchers have suggested that an abnormality in trophoblasts might result in shallow placentation and inadequate transformation of the spiral arteries, leading to pre-eclampsia (35). Two independent group of investigators began studying the placental bed in late 1950's. The first team comprised of Dixon and Robertson who worked in Jamaica (36) and the second team comprised of Renaer and Brosen from Belgium (36). They studied the placental bed

by biopsy. The histological confirmation that the biopsy was obtained from placental bed was based on following findings:

1) The presence of trophoblast
2) Adherent villi
3) Transformed spiral arteries

The specimen included uteri from women who had Preeclampsia, Preeclampsia with IUGR, chronic hypertension and nephrotic syndrome. These studies gave the initial assessment of changes in placental bed which is now defined in an entity called The Great Obstetrical Syndrome.

Role of placenta in normal pregnancies

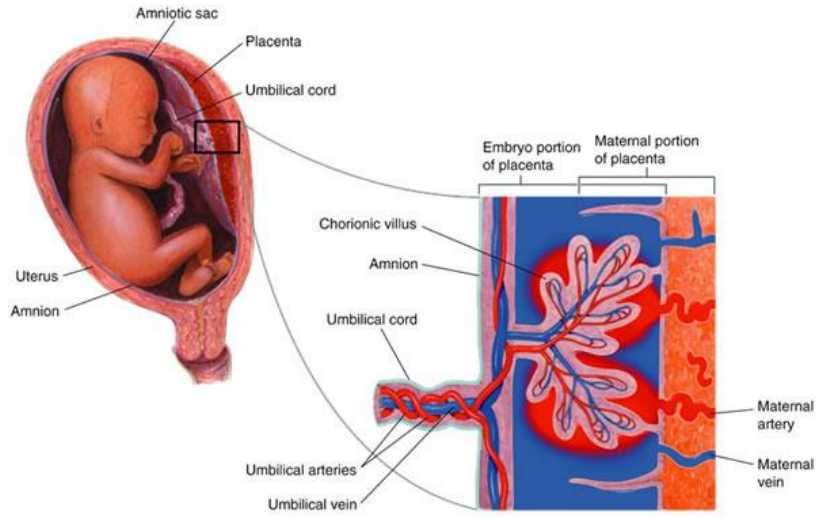


Figure 2: Normal placenta and chorionic villus(38)

Placentation and trophoblastic invasion of maternal tissue involves two processes. First is vascularisation, to establish Foeto-placental vascular network and secondly, invasion of maternal spiral arteries by cytotrophoblasts or endovascular trophoblasts(39).

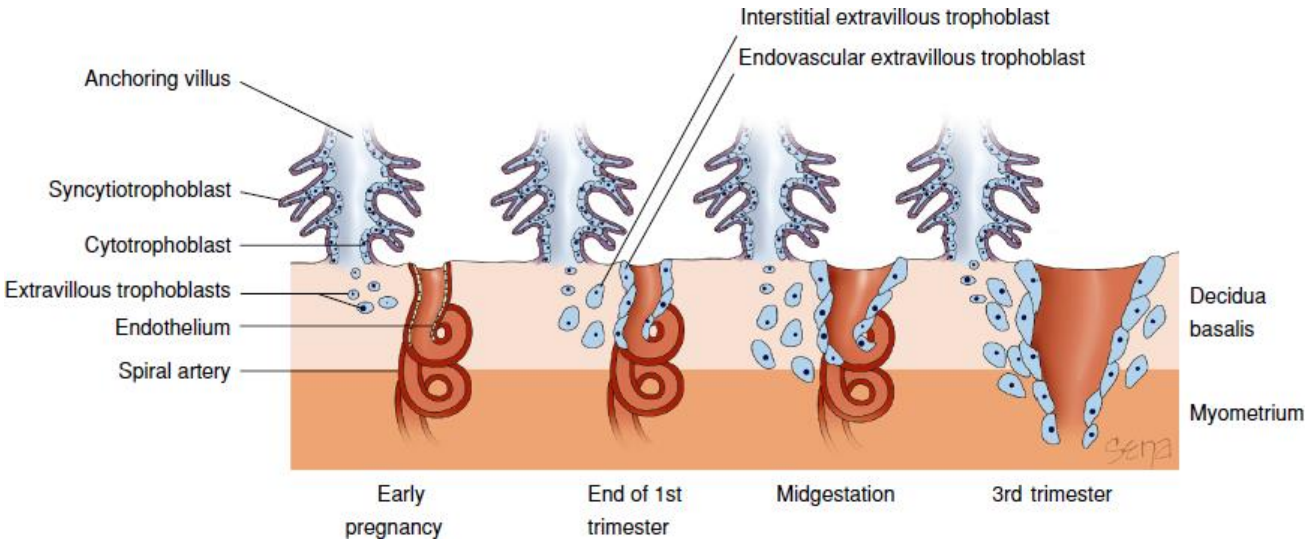


Figure 3: Spiral artery remodelling during pregnancy (37)

During early gestation, at the time of implantation, trophoblastic tissue differentiates into cytotrophoblast and syncytiotrophoblast. The cytotrophoblast invades the decidual, junctional zone myometrial segments, inner third of myometrium and the spiral arteries. These trophoblast induce remodelling of the latter perhaps by causing loss of elastic lamina , most of the smooth muscles and temporarily replacing the endothelial cells(39). This transformation then helps in turn to transform a high resistance system into a low resistance, high flow type which is essential for normal growth of the foetus (40). So by nature, the endothelial cells are replaced by cytotrophoblast which in turn results in replacement of endothelial like receptors with maternal adhesion molecules such as vascular endothelial (VE) cadherin vascular adhesion molecule- 1, platelet -endothelial molecule -1 and integrin (39). This mechanism also accounts for prevention of foetal cell rejection by maternal cells. The trophoblast takes up the phenotype of endothelial cells and are in direct contact with

the maternal blood therefore the maternal and foetal cells do not mix. According to Brosen et al, trophoblastic invasion of spiral artery is preceded by oedema of vessel wall, disintegration of elastic fibres and changes in smooth muscle layers ultimately leading to loss of myofibrils (34). This contrasts the common belief that its the trophoblastic cells which causes disintegration of the elastic fibres and loss of myofibril. In addition, development of the foetus initially occurs under low oxygen tension while the placental perfusion is only from intervillous space; unplugging of maternal spiral arteries happen after 12 weeks of gestational age(41). Numerous factors such as cytokines, growth factors, oxygen tension and local cellular environment- immune cells such as macrophages and decidual natural killer cells helps migration of trophoblastic cells (42). Defects in deep placentation are associated with a spectrum of obstetrical syndrome which includes Pre-eclampsia, IUGR , Preterm labour with intact membrane, Preterm PROM , Abruptio placentae and Mid trimester abortion. These disorders are characterised by -the degree of restriction of transformation of spiral arteries and presence of arterial lesion in JZ myometrium of the placental bed.The degree and extent to which physiological transformation of spiral arteries varies according to the placental bed area and is more in the centre than in the periphery. In normal pregnancy around 90% of spiral arteries are fully transformed.

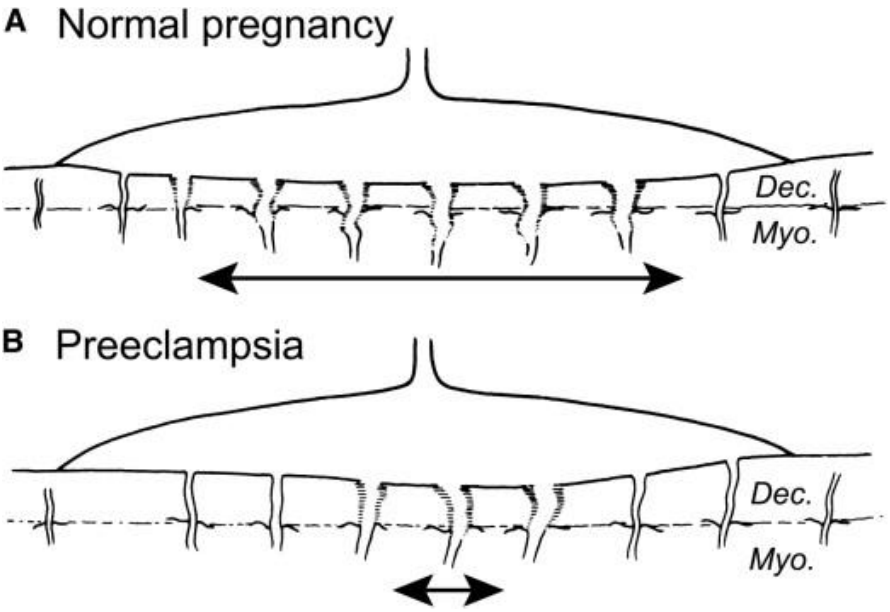


Figure 4: A. Normal placental bed with full transformation of the myometrial spiral arteries except at the periphery of the placental bed B. Defective deep placentation is characterized by nontransformation of the myometrial spiral arteries reducing the central area with deep placentation(34).

Three different kind of spiral artery transformation can be identified in JZ myometrium:

1) Partial transformation

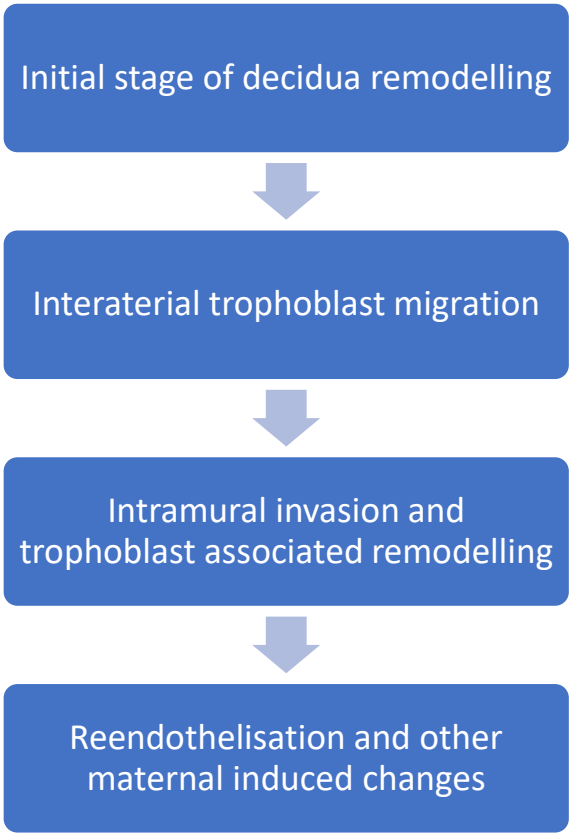
2) Absence of transformation.

3) Absence of transformation with obstructive lesions

In preeclampsia, the physiological transformation of spiral arteries is reduced in central placental bed. In preeclampsia with IUGR, defective deep placentation is frequently observed with non- transformed spiral arteries having obstructive lesion. In

preterm labour and IUGR without hypertension, the defective placentation is observed with obstructive lesion of non- transformed spiral arteries in Junctional myometrium.

Remodelling of spiral artery has been described as multi step process which starts at the beginning of pregnancy(43).



The precise mechanism of defective remodelling is not known. It is logical to assume that different clinical condition can lead to various defects of transformation and result

in different defects of placentation. Association of partial transformation with preterm delivery and preterm PROM suggest that placentation disorder in preeclampsia is more severe and begins early in gestation(44).

2. Maternal maladaptation and inflammatory response

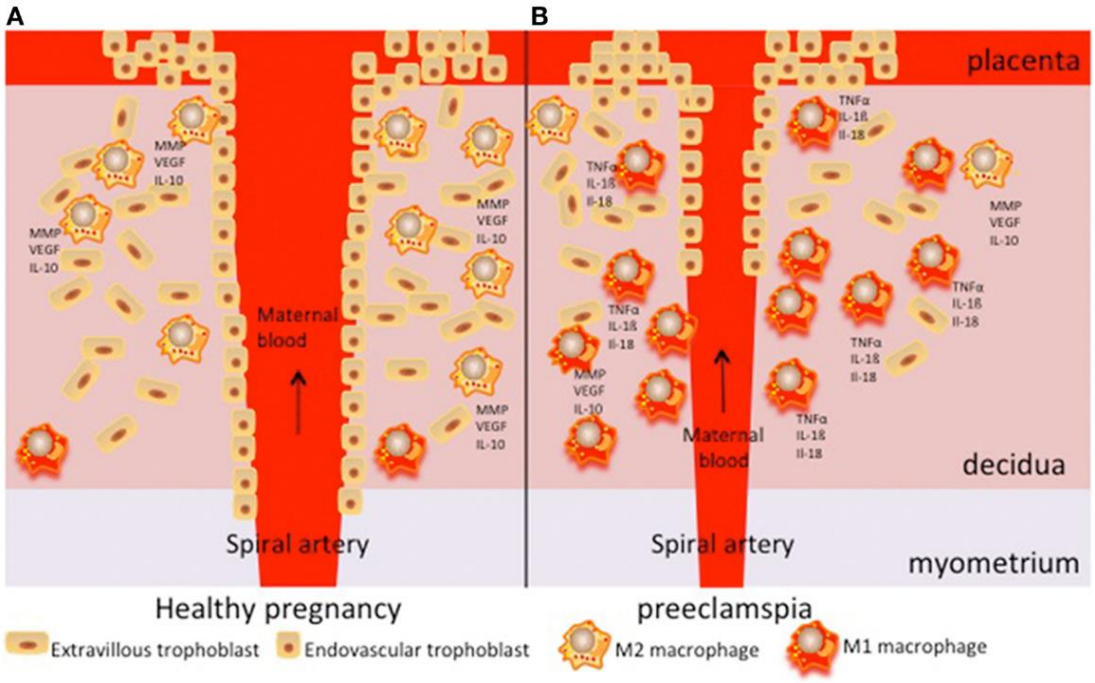


Figure 5 : Schematic overview of the role of decidual macrophages in pregnancy(A) and pre-eclampsia(B)(44)

The foetal trophoblastic cells are regarded as allo-antigen to which mother mounts a low grade systemic inflammatory response (45,46). Syncytiotrophoblastic microparticles in maternal circulation could be the cause. (47) However it is already known that utero placental perfusion only begins by the end of first trimester while increased levels of syncytiotrophoblastic particles are detected in the second and third trimesters (48). The initial inflammatory response in first trimester is due to

interaction between decidual immune cells and trophoblastic cells and in later trimester is due to syncytioblastic particle released into maternal vascular system.(49). Recently Brosen et al. has suggested that the process of cyclical decidualisation, serves as a mechanism to prepare the uterus for deep placentation. Both menstrual and inflammatory conditions cause physiological ischemia-reperfusion stress, albeit much more so in pregnancy. The authors have speculated that cyclical menstruation may have a critical role in protecting uterine tissue from profound inflammatory and oxidative stress associated with deep placentation. This process is called as Preconditioning. More so, it is interesting to note that in normal pregnancy, induced fragmentation of the internal elastic lamina of myometrial spiral arteries persist beyond first pregnancy which explained higher birth weight in subsequent pregnancies (50). This explains the well observed fact why teenage primigravida are associated with significant increased risk of complications such as preterm deliveries, foetal growth restriction and preeclampsia in comparison with primigravida in early twenties, in whom preconditioning has occurred(51). The association of obstetrical syndromes with different vascular diseases in junctional myometrium suggest that preconditioning of this zone at the time of conception is the critical factor for successful implantation and development of normal placentation. As suggested by Romero et al. more than one mechanism of disease may lead to defective deep placentation and common pathophysiologic consequence is ischemia (52). The timing and extent of ischemia as well as host response in both the mother and the feotus gives rise to different clinical phenotypes. Environmental and genetic factors as well as the time of onset, extent and duration of the ischemic injury may play an

important role in determination of the type of phenotype. Arriving at a similar conclusion, Robert and Hubel proposed that the factors that increased the risk of preeclampsia is also associated with abnormal implantation (53). Progress in understanding the molecular processes that occur during implantation indicates that among other maternal constitutional factors, the process of endometrial decidualisation and angiogenesis is a target for pre-pregnancy diagnosis and therapy. Therefore, the characterisation of angiogenesis and development of biomarkers in early placental development will in future provide diagnostic and hopefully invasive predictive markers to identify women at risk of developing defective deep placentation syndrome such as Preeclampsia, IUGR, Preterm birth and other pregnancy outcomes. A classification which appropriately classifies defective deep placentation also has important implications for feto-placental research and research of placental diseases with imaging techniques. Though it may be said that placental biopsy may not be representative of entire vascular placental bed, some authors have attempted to standardise the technique by using ultrasound directed target biopsy of centre of placental bed(54).

Colour doppler and spectral doppler ultrasound studies of spiral arteries also have a limitation because they do not address the lateral extent of spiral remodelling. This means that the conclusion of non-invasive studies should be interpreted with caution(55,56).

The Great obstetrical syndrome is associated with defective deep placentation which maybe associated with different degrees of restricted remodelling and obstructive lesion in spiral arteries. This concept maybe used to improve our understanding of the

characterisation of placental bed disorders and will be valuable in refining the existing tools for assessment of risk before adverse pregnancy outcomes(34)

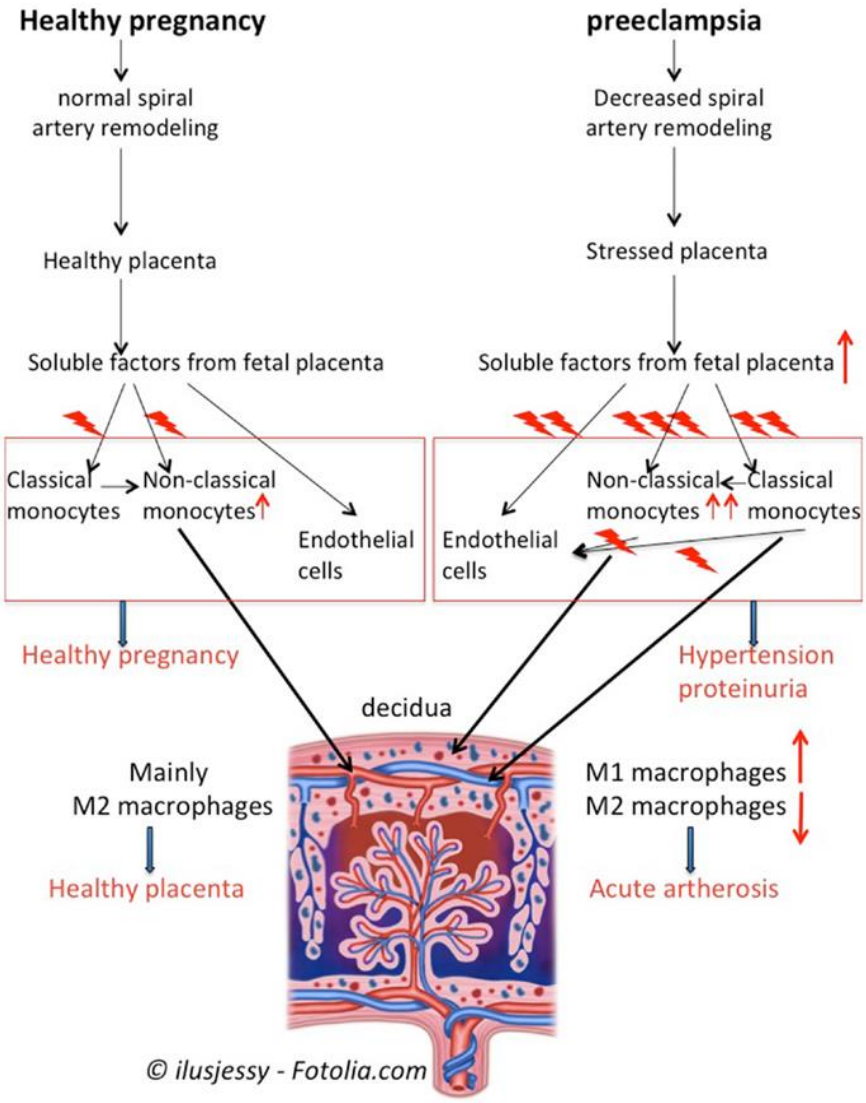


Figure 6: Summary of monocytes and macrophages in pregnancy and preeclampsia(44)

3. Placental hypoperfusion and hypoxia

In preeclampsia, it is established that there is reduced blood flow to the placenta because of defective remodelling and acute artherosis (57). In vivo techniques magnetic resonance imaging and doppler studies have established that it is mostly seen in early onset pre-eclampsia rather than late onset Pre-eclampsia (58). The defect in spiral artery remodelling in pre-eclampsia is restricted to the distal segments of spiral arteries that is the proximal decidua and junctional zone myometrial segments. Hence the arteries in the myometrial spiral arteries still have their smooth muscle and elastic lamina with absent or partial transformation of arteries(34,46). The exact mechanism of why this happens is not known but various factors such as genetic variation, biology of trophoblast or defective trophoblastic differentiation together with extrinsic factors such as maternal constitutional factors, action of macrophages, defence mechanism, impaired action of natural killer cells are proposed to be responsible (42,57). It also has been proposed that proteolytic activity of different population of extra villous trophoblasts could be the reason for invasion of decidua and spiral arteries (59). It is believed that reduced placental blood flow results in placental hypoxia which has been suggested as a cause for preeclampsia (45,60). This hypothesis has no experimental confirmation as in vivo there has been no measurement of in vivo oxygen tension in intervillous space (61). Having said all this, it is also believed that reduced blood flow or chronic hypoxia are not the direct cause of placental lesion as seen in preeclampsia but is just a contributing factor. It has been assumed that the lesion could rather be due to an ischemia -reperfusion or

hypoxia – reoxygenation type of injury caused by free radicals such as reactive oxygen species. It also has been speculated that intermittent blood flow to intervillous space could be responsible for hypoxia reoxygenation injury (21). This has been furthermore supported by Yung Et al in 2014, who showed that high levels of activation of unfolded protein response pathways due to hypoxic- reperfusion injury to endoplasmic reticulum occurred in placental samples taken from early and late onset preeclampsia (62). Accumulation of aggregates of unfolded protein or misfolded proteins has been observed in placentas of pre-eclamptic patients and is proposed as the pathophysiology of it (63). The hypoxia of normal pregnancy is worsened by defective spiral arteries (64). The Hypoxia Reperfusion damage to placenta causes re apoptosis and release of excess placental debris compared to normal pregnancy (65).

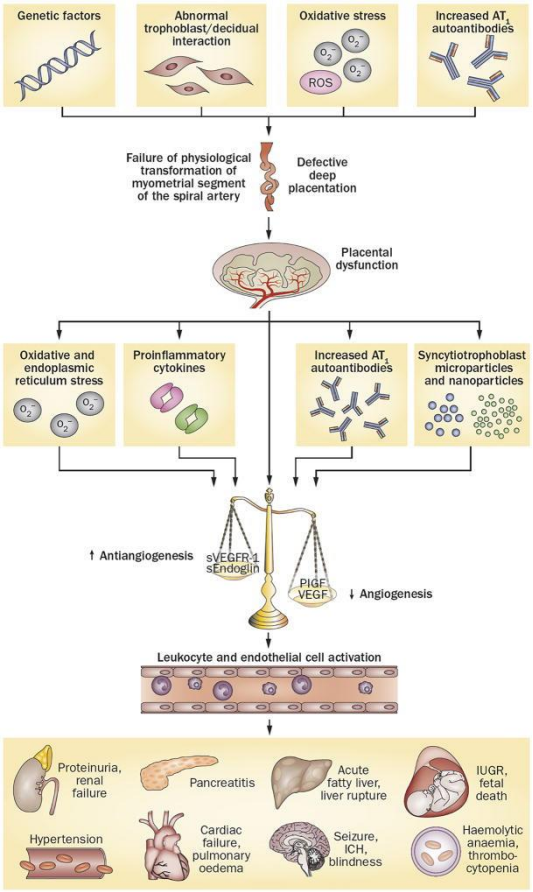


Figure 7: Integrated model of complex pathophysiology of preeclampsia(66)

4.Immunological factors

There is increasing evidence that imbalance between Pro-angiogenic and anti-angiogenic factors are responsible for pathophysiology of Preeclampsia (67). The indicators of angiogenic factor imbalance appears before clinical signs are apparent (68). However it is not known why some women develop pre-eclampsia while others with similar factors develop SGA neonates without any symptoms (69). Increased levels of sFlt-1 and decreased VEGF and PLGF has been seen in sample taken at time of delivery in Pre-eclamptic patients (70). Cross sectional studies done in African women at term before delivery showed that there is an association of pro-angiogenic (PIGF and TGF-beta) and Anti-angiogenic (sEng and sFlt-1) factors and Preeclampsia (71). In a similar study, sFlt-1 concentration were significantly high in early onset preeclampsia and higher in late onset Preeclampsia compared to normotensive controls and chronic hypertensives while VEGF was not detectable in any group. (71) Significantly higher plasma levels were seen at 23 and 30 weeks of gestational age both in late and early onset Preeclampsia when compared to normal pregnancies while sFlt -1 rises by 26 to 29 weeks(72). A pilot study conducted by Thandhani et al. which removed sFlt-1 extracorporeally from pre-eclamptic women between gestational age of 27 to 31 weeks lowered the blood pressures and reduced proteinuria and other complications (73) The levels of anti-angiogenic factors such as sEng and sFlt-1 and proangiogenic VEGF,PIGF and TGF-beta are generally known to cause maternal endothelial dysfunction, leading to hypertension, renal endotheliosis and blood coagulation,

Physiological transformation of the spiral arteries is neither specific to pre-eclampsia nor adequate to cause it.(34) It also has been seen in other obstetric syndromes-including spontaneous abortion,(74,75) IUGR,(76,77) foetal death,(75) placental abruption,(78) preterm labour(79) and preterm premature rupture of membranes(44). The mechanisms accountable for failure of physiological transformation of the spiral arteries have not been fully explained. It is believed to result from inadequate placentation resulting in increased levels of various vasoactive peptide, exemplified by the soluble receptor for various endothelial growth factor, commonly referred as soluble FMS- like Tyrosine kinase 1 (sFlt-1)(70). Recent studies indicate that elevation of sFlt – 1 present in patients of preeclampsia and eclampsia is not seen in gestational hypertension(81). These differences are due to various underlying mechanism which later predisposes to Cardiovascular diseases.

5. Genetic Factors

From a hereditary point of view, pre-eclampsia is multifactorial and polygenic. In a comprehensive review by Ward and Taylor, the incident risk of pre-eclampsia was 20-40% for daughters of preeclamptic mothers and 22 to 47% for twins(80).

Candidate genes and predominant polymorphisms implicated in the pathogenesis of pre-eclampsia (81)

Proposed mechanism	**Gene name**	**Gene symbol**	**Polymorphism**
Vasoactive proteins	Angiotensinogen	*AGT*	235Met > Thr
	Angiotensin converting enzyme	*ACE*	I/D intron 16
Thrombophilia and hypofibrinolysis	Factor V Leiden	*F5*	506Gln > Arg
	Methylenetetrahydrofolate reductase	*MTHFR*	C667T
	Prothrombin	*F2*	G20210A
	Plasminogen activator factor-1	*SERPINE1*	Promoter insertion/deletion
	Integrin glycoprotein IIIa	*GPIIIA*	C98T
Oxidative stress and lipid metabolism	Apolipoprotein E	*APOE*	C886T
	Microsomal epoxide hydrolase	*EPHX*	113Tyr > His
	Glutathione-S-transferase	*GST*	A313G

Maternal Risk factors

A meta-analysis published in BMJ 2016 by Emily et al (82) identified risk factors, which if detected prior to 16 weeks can estimate the relative risk factor of developing pre-eclampsia.

RISK FACTORS	RELATIVE RISK
Prior preeclampsia	8.4
Chronic hypertension	5.1
Pre-gestational diabetes	3.7
Multifetal pregnancy	2.9
Pre-pregnancy BMI >30	2.8
APLA	2.8
SLE	2.5
Prior still birth	2.4
Nulliparity	2.1
Pre-pregnancy BMI >25	2.1
Prior placental abruption	2.0
Chronic Kidney disease	1.8
ART	1.8
Maternal age >40 years	1.5
Prior IUGR	1.4
Maternal age >35 years	1.2

BMI is considered a moderate risk factor even though the risk of predisposition to Hypertensive disorder with maternal BMI more than 30 kg/m2 is similar to APLA or SLE. Both APLA and SLE are considered major risk factors for the development of pre-eclampsia and in the presence of these two, preventive prophylaxis is advised.(83) More important fact to note is that pre- pregnancy BMI is a modifiable risk factor while others are not.

Predictors of Preeclampsia

Historical risk factors can predict about 30 percent of women who will develop hypertensive disorders of pregnancy(84). The present area of active interest is the use of laboratory and imaging tests in combination with historical risk factors to calculate a woman's risk of developing preeclampsia. However, the current models have low positive predictive values.

Provocative biophysical tests: Biophysical test such as Angiotensin II challenge test(85,86), Roll over or supine pressor test, Isometric exercise or hand grip test were the test used in the past for the prediction of pre-eclampsia. However, these were found to be time consuming and unreliable for prediction.

Obesity

High prevalence of overweight and obesity increases the vulnerability of women in reproductive age to hypertensive disorders of pregnancy. In developing countries including India , the epidemic of obesity is seen along with continuing problems of undernutrition, creating a double burden(87,88). Wang et al. analysed data from National Family health survey (NFHS, 1992-1993,1998-1999 and 2005-2006) to observe the trends and prevalence of underweight, overweight and obesity in recent decades in India. The data discovered that compared to overweight, underweight continues to remain high. Overweight seemed to be more prevalent among women in the urban setting and those belonging to high SES groups. Even though the incidence in overweight and obesity has only slightly increased all over but it has increased significantly in the higher SES and urban population (89). Mitchelle et al. collected data from 36 developing countries of women between the age group of 20-49 years- the data revealed that young women residing in both urban and rural areas had more prevalence of overweight than underweight women, especially in countries at higher levels of socioeconomic development. The data from India suggested that there were 26.4 % women who were overweight in urban areas as compared to 5.6% in rural areas. On other hand women who were underweight in urban area comprised of 23.1% while in rural area it was alarmingly high at 48.2% (90). Another survey which was conducted in three countries namely India, Bangladesh and Nepal- obesity and overweight problems have risen in females in reproductive age group.(91) This rise in

women with higher BMI results in increase in population which is at high risk for developing hypertensive disorders of pregnancy.

In a metanalysis done from 40 studies from Europe and 30 from America , it was shown that even though prior gestational hypertension, chronic hypertension and antiphospholipid syndrome are absolute risk factors, when population attributable risk is considered, then nulliparity and obesity (BMI >30kg/m2) accounted for largest population risk.(82) The complex interplay of these factors leads to the essential pathophysiology of the preeclampsia, that is ischemia and hypoxia of placenta.(16)

Pre-pregnancy inflammatory and cardiometabolic risk factors predict the risk of hypertensive disorders of pregnancy. Obese women are at a higher risk of developing hypertension in pregnancy. The odds of having hypertension in pregnancy are 1.8 times greater in women who are hypertensive but not obese before pregnancy and the odds of having hypertensive complication in pregnancy is 3.5 times higher in women with both obesity and hypertension in the pre- pregnancy period (92). Even in industrialised countries approximately 50% of the pregnancies are not planned, which limits the ability to identify women with cardiovascular disease risk factors before pregnancy. Screening of women for hypertension in the age group of 18- 44 years is low even in developed countries. 15% of the women who were screened were seen by a general physician, while much higher proportion 62% were seen by gynaecologist and 23% by both. It was also noted in the study that women who were screened by gynaecologist received more counselling and preventive services than that given by the general physicians (93). The same survey also illustrated the fact that there is

limited knowledge about pre- eclampsia and future risk in reproductive age women among all specialities. A national vital statistics survey done in United States stated that even though pregnancy rates have changed very little from 1990 in women aged 25 to 29 but the rates have increased in women in their 30s and 40s. In the past 45 years, the prevalence of obesity in reproductive age group has dramatically increased. Currently in the United States, 45% of pregnant women are either overweight or obese and this has statistically doubled in the past 30 years. Once pregnant, 43% women gain more than the recommended weight (94). Obesity contributes to development of high risk conditions in pregnancy such as gestational diabetes, hypertensive disorders, macrosomia and increased perinatal complications. Many epidemiological studies have correlated obesity and hypertensive disorder of pregnancy. In a large metanalysis published in BMJ in 2016 the pooled rates of preeclampsia was found high in women with BMI more than 30 than in women with BMI less than 30 (82). The leading attributable risk factor for development of preeclampsia is obesity, with severity of preeclampsia having a dose dependent association with higher classes of BMI(95). A large population based cohort study showed an incremental rise in preeclampsia with obesity (96). In a retrospective study, irrespective of the parity it was seen that women who developed preeclampsia had high BMI both before and after delivery, while cholesterol (both total and LDL) was significantly raised after delivery (97). It has been estimated that around 30% of the association between preeclampsia and obesity is facilitated through atypical inflammatory profiles signified by elevated *C*-reactive protein (CRP) levels. It is a mediator for inflammation, which is produced by liver and adipocytes that can cause cardiovascular morbidities (98).

Dyslipidemia and Preeclampsia

Physiological hyperlipidaemia is associated with pregnancy which is not atherogenic but is believed to be under hormonal control (99). In women with preeclampsia, the severity of dyslipidaemia is much more than normotensive patient (13).

Lipid profiles have been documented throughout pregnancy in both pregnancy complicated by hypertension and Normotensive pregnancy. Despite this, there is no standard reference for lipids and lipoprotein during pregnancy (6). The increased insulin resistance seen in pregnancy is in turn reflected in lipid and lipoprotein profiles of the mother. After 6 weeks of gestation the lipid levels drop slightly followed by an increase in each trimester. Triglyceride and Cholesterol increase sharply during pregnancy, still on an average the levels do not exceed beyond 250mg/dl. Pregnancies are noted to get complicated by gestational hypertension, preeclampsia, preterm birth and large for gestational age babies when the level exceed 300 mg/dl (100). Triglyceride levels are increased through hepatic stimulation of production of Very low-density lipoprotein (VLDL) and inhibition of lipoprotein lipase both in the liver and adipose tissue which is mediated by oestrogen. This physiological increase in the lipids and lipoprotein levels are aimed at accommodating increasing foetal demands of growth and development (101). Pre-eclampsia is characterised by endothelial dysfunction. The exact mechanism for this dysfunction is still unclear. It can be speculated to be due to increase in triglyceride and free fatty acids level. Triglyceride, Apo B and small LDL particles are all increased in preeclampsia which causes

increase in vascular cell adhesion molecule which is in turn an indicator of endothelial dysfunction (20).

Belo et al. in their study reaffirmed that pre-eclamptic women showed, in third trimester, higher mean serum triglyceride concentration and lower high density lipoprotein cholesterol. They emphasized that this 'atherogenic' lipid profile in pre-eclamptic females perhaps is a potential contributor to endothelial cell dysfunction (11). Kokia-E et al found that the TG and LDL level were significantly higher in severe pre-eclampsia group. He also concluded that the lipid profiles in hypertensive pregnant women could be associated with enhancement of pathological lipid deposition in predisposed vessels such as uterine spiral arteries (102).

Levels of very-low density lipoproteins and non-HDL-C are also significantly higher among pre-eclamptic women than among normotensive women, suggesting that, although LDL-C levels may not be the most useful measure for preeclampsia prediction, a combined measure of all types of non-HDL-C may be useful (103).

In India, Usha Adiga et al. conducted a study at Mangalore which showed 20% rise in total cholesterol, 27% decrease in HDL cholesterol levels in women with preeclampsia (104). Serum TG and VLDL levels were significantly higher in severe PE group as in comparison with mild PE group, while there is no significant difference on other lipid parameters (CH, LDL, and HDL)(105). Wladimiroff et al did a prospective cohort study which showed that women with serum cholesterol concentration >6mmol/L (>233mg/dl) experienced fivefold increased risk of preeclampsia than women with <5 mmol/L (<194mg/dl) after accounting for confounding maternal BMI and gestational age(10). In another study done by

Lorentzen et al, 19 women who developed Preeclampsia had higher level of triglycerides at 16-18 weeks than women who were normotensive(8). William et al did a study among sub Saharan African women and reported an inverse association between risk of developing preeclampsia and HDL cholesterol concentration (106). In a case control study, Ware-Jauregui et al showed that women with triglyceride concentration >284mg/dl had a five- fold increased risk of developing pre-eclampsia than women with triglyceride concentration of <189mg/dl (107). Low preconceptional levels of HDL-c and high levels of triglycerides are independently associated with an increased risk for preeclampsia and /or gestational diabetes mellitus, while the highest rates of this composite outcome were observed in a group with both high triglycerides and low HDL-c (108).

The association between lipid levels during pregnancy and pre-eclampsia have suggested measuring lipid levels in all pregnant women as a means of early-pregnancy "screening" for the identification of women who may be at higher risk for development of this disease.

The problem is that diagnosis of hypertensive disorders is not very straight forward as it seems. Even the well-defined criteria that is defined BP >/140/90 mmHg performed 6 hours apart has fallacies of its own. According to the Seventh Report of the Joint National committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure, individuals with systolic blood pressures of 120-139mmHg or/and Blood pressure of 80-89 mmHg should be considered pre-hypertensive (109). This might imply that a threshold of 140/90 mmHg might be high for any population, especially young women of childbearing age leading to underestimation of

hypertensive disorder of pregnancy. Blood pressure also changes as gestation progresses and is lowest in mid trimester, even in patients of chronic hypertension making it difficult to diagnose hypertensive disorder of pregnancy (110). Women with chronic hypertension may be labelled as gestational hypertension, when by the third trimester the BP increases to pre-pregnant levels with the former being diagnosed in retrospect after gestational hypertension fails to normalise 12 weeks after delivery. Pre-eclampsia may occur de novo in in previously normotensive women or can be superimposed on chronic hypertension.

MATERIALS AND METHODS

TYPE OF STUDY: Nested case control Study

Scheme of Research:

Women presenting to antenatal OPD of Obstetrics Department, Christian Medical College with singleton pregnancy, and Gestational age less than 16 weeks (G.A. confirmed by first trimester ultrasound scan) and those planning to deliver in CMC were approached. Patient information sheet was given and they were recruited into the study after informed consent. Morning fasting lipid profile was collected. The collected samples were centrifuged and the serum was stored in Biochemistry lab at -80˚Celsius. Patients were followed up till after delivery.

Definition:

Case: After the initial recruitment, a case was defined as a woman who developed

Hypertensive disorder of pregnancy. The stored sample was then analysed for lipid profile.

Control: The control was defined as a woman who did not develop any hypertensive disorder of pregnancy and whose BMI matched the case. The control was randomly selected from all women whose samples were collected. This sample was also sent for analysis of lipid profile.

Inclusion criteria

All Pregnant women, age ranging from 18-34 years

Gestational age <16 weeks

Exclusion criteria

GA >16 weeks

Age >35 years

Multiple gestation

Chronic hypertension

Other systemic causes of hypertension- renal causes, collagen vascular diseases, etc

Pre-gestational diabetes mellitus

APLA Positive with recurrent abortions

Thrombophilia of pregnancy

Variables Analysed:

a) Blood pressure: Measured by Heines manual sphygmomanometer in sitting position at mid arm level with size appropriate cuff.

Hypertensive disorder of pregnancy was classified according to ACOG guidelines 2013

Chronic hypertension

- Blood pressure ≥140/90 mmHg before pregnancy and at <20 weeks of gestation, or diagnosed for the first time during pregnancy and does not resolve postpartum

Gestational hypertension

- New-onset blood pressure ≥140/90 mmHg detected at ≥20 weeks gestation without proteinuria
- Pre-eclampsia does not develop and blood pressure returns to normal by 12 weeks postpartum

Pre-eclampsia and eclampsia

- Blood pressure ≥140/90 mmHg on two occasions at least 4 h apart or ≥160/110 mmHg within a shorter interval (minutes), at ≥20 weeks of gestation, in women with previously normal blood pressure and proteinuria*
- In the absence of proteinuria, new-onset hypertension plus new onset of any of the following features: serum creatinine concentrations >97 μmol/l or doubling of serum creatinine concentration in the absence of other renal disease; elevation of liver transaminases to twice normal concentration; pulmonary oedema; and cerebral or visual symptoms

- Eclampsia: seizures in women with pre-eclampsia that cannot be attributed to other causes
- Atypical form of preeclampsia presents with systemic symptoms , abnormal haematological tests or elevated liver enzymes without proteinuria

Pre-eclampsia superimposed on chronic hypertension

- Women with hypertension (at <20 weeks gestation) and new-onset proteinuria*
- In women with hypertension and proteinuria* (at <20 weeks gestation), development of any of the following features: sudden increase in proteinuria;* sudden increase in blood pressure in women whose hypertension was previously well controlled; thrombocytopenia (platelet count <100,000 per mm^3); and elevated liver transaminase levels

*Defined as urinary protein excretion ≥300 mg/24 h, a total protein:creatinine ratio ≥30 mg/mmol (or ≥0.3 when both are measured in mg/dl) or a dipstick reading of ≥1+ (only if other quantitative methods are not available).

b) BMI: Weight in Kgs /height in m2

Height as measured in centimetre by a wall mounted Stadimeter.

Weight as measured in Kilogram by Bathroom weigh scale

Body Mass Index: Proposed Asian Criteria		
Classification of Obesity	Body Mass Index (kg/m2)	
	Proposed Asian Criteria	Previous WHO criteria
Underweight	<18.5kg/m2	<18.5kg/m2
Normal Range	18.5 to 22.9 kg/m2	18.5 to 24.9 kg/m2
Overweight	23 to 24.9 kg/m2	25 to 29.9 kg/m2
Obese	>25 kg/m2	>30 kg/m2

Adapted from *The Lancet* 2004:363:157-63

c) Diet: Non vegetarian / Vegetarian

d) Gravida :

Primigravida: A woman pregnant for the first time.

Multigravida: A pregnant woman who has been pregnant before.

e) Lab analysis: Lipid Profile

Maternal fasting samples, collected in 10 ml Vacutainer tubes (Becton, Dickson and Co., Franklin Lakes, NJ) at gestational age below 16 weeks. The collected samples were centrifuged and the resultant plasma was stored at -80◦C until analysis.

Plasma was analysed after an average of 6 to 9 months for lipid profile which included Total cholesterol, LDL, HDL, Triglycerides.

Cholesterol: (Coefficient of variation of total cholesterol testing -2.2%) Endpoint enzymatic colorimetric assay with cholesterol esterase, cholesterol oxidase and peroxidase in Roche P800 auto analyser.

HDL: (Coefficient of variation of HDL testing -2.8%) Endpoint enzymatic colorimetric assay with PEG cholesterol esterase, PEG cholesterol oxidase and peroxidase in Roche P800 auto analyser.

LDL: (Coefficient of variation of LDL testing -6%) Differential solubilisation with no pre-treatment, Endpoint enzymatic colorimetric assay with cholesterol esterase, cholesterol oxidase and peroxidase in Roche P800 auto analyser.

Triglyceride: (Coefficient of variation of Triglyceride testing -3.5%) Endpoint enzymatic colorimetric assay with lipase, glycerokinase, glycerol phosphate, glycerol phosphate oxidase and peroxidase in Roche P800 auto analyser.

Sample size calculation:

Analysis of the past 5 years audit in our institution showed an average of 10% of all pregnancies to be complicated by hypertensive disorders. To obtain a difference of 40% between the proportion of dyslipidemia among subjects with and without hypertension with 80% power and 5% significance, a sample size of 20 subjects with hypertensive disorder was needed.

$$H_0 : P_1 = P_2; \qquad H_a : P_1 \neq P_2$$

$$n = \frac{\left\{ Z_{1-\frac{\alpha}{2}} \sqrt{2\,\bar{P}\,(1-\bar{P})} + Z_{1-\beta} \sqrt{P_1\,(1-P_1) + P_2\,(1-P_2)} \right\}^2}{(P_1 - P_2)^2}$$

Where,

$$\bar{P} = \frac{P_1 + P_2}{2}$$

P_1 : Proportion in the first group

P_2 : Proportion in the second group

α : Significance level

$1-\beta$: Power

A cohort of 222 women were recruited and followed up. Of these 20 developed hypertensive disorders.

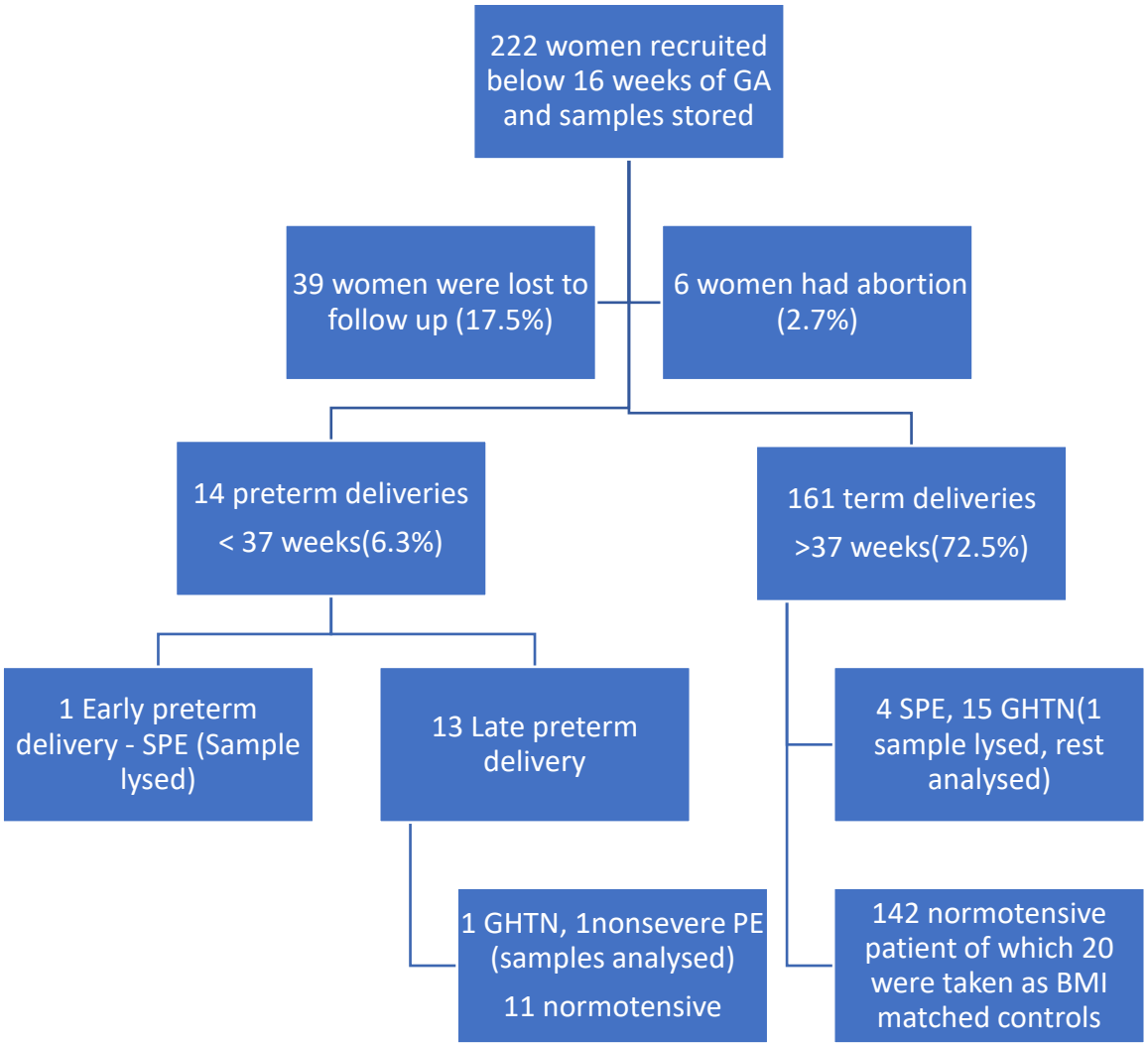
Time Period of study: August 2017 to November 2018

No. of Samples recruited: Cases 20, control 20 from a cohort of 222 women.

RESULTS AND ANALYSIS

The study recruited 222 antenatal women attending the OPD who consented to the study. All had a singleton pregnancy and were less than 16 weeks gestation.

Overall distribution



1. Age distribution

The age distribution among cases was from 24 to 35 years with a mean age of 28 years, while in the control group the ages ranged between19 to 33 years with an average age of 24.68 years. (*p* value-0.005)

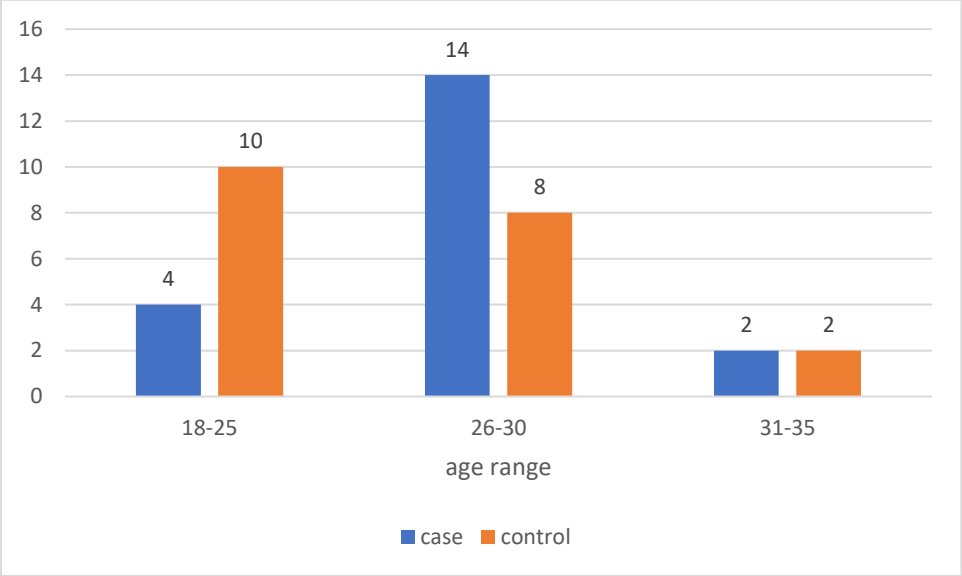


Figure 8. Age distribution:

Maternal age (years)		
	cases	Controls
Mean ± SD	28±3.277	25±3.774
Range	24-35	19-33

Standard error	.733
95%confidence interval of the difference	1.088-5.612
p value	0.005

2. Obstetrical score

There were 52.5% multigravidas and 47.5% primigravidas. Amongst cases and controls there was similar distribution in parity. For cases, 55% were Primigravidas and 45% were multigravida and for controls both were equally distributed -50 % each.

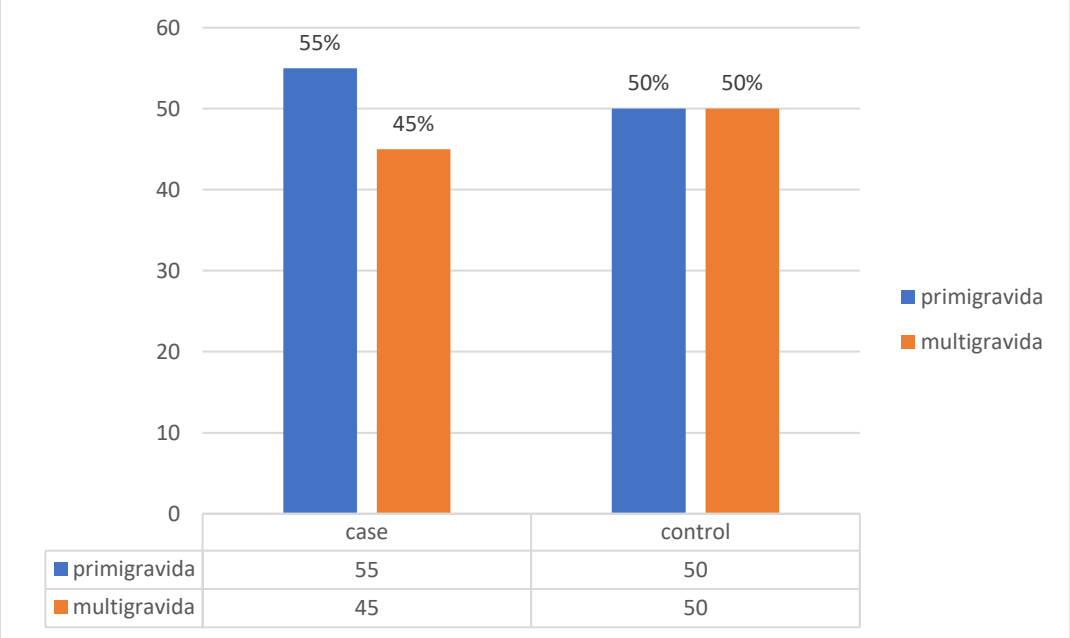


Figure 8. Obstetrical score:

3. Diet

95% of the women recruited were non-vegetarians. There were only 5% vegetarians, both being equally distributed among cases and controls, that is each 2.5%.

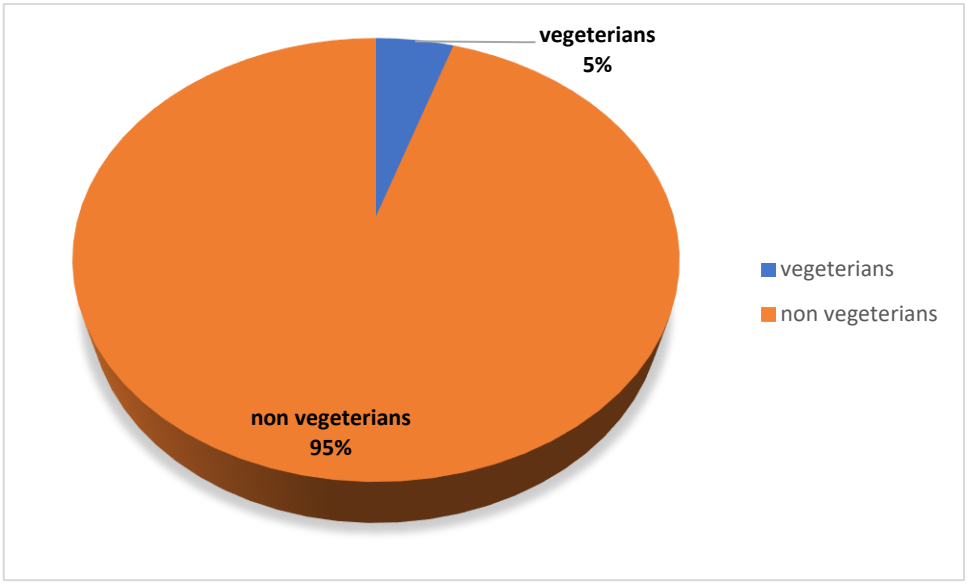


Figure 9. diet distribution.

4. Body Mass Index

The distribution of BMI is mentioned for cases as the controls were BMI matched at delivery. 50% of women with hypertensive disorders of pregnancy were obese (n=10), 30 % (n=6) were overweight while only 10% (n=2) each were in normal weight and underweight category.

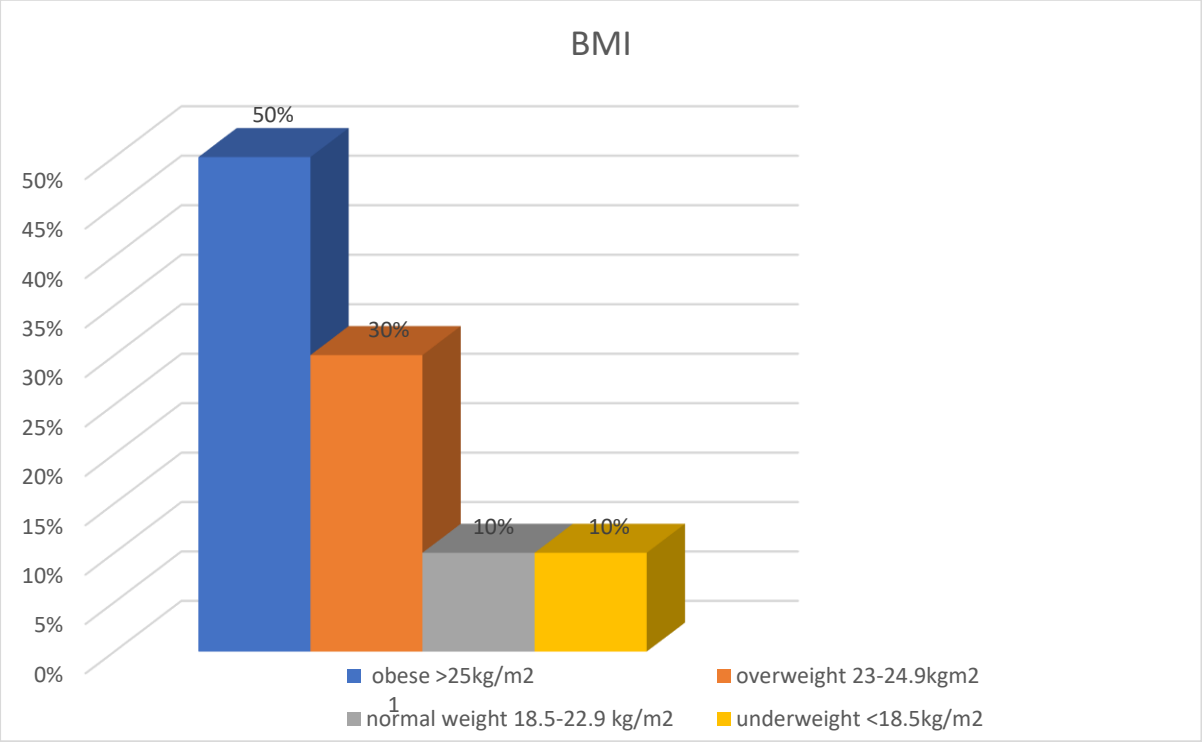


Figure 10. BMI distribution for cases: Measured at 16 weeks

BMI kg/m2		
	cases	controls
Mean ± SD	24.8±4.137	24.8±4.021
Range	17-31	17-30

5. Mode of Delivery

Of the total deliveries- 60 % were normal vaginal deliveries along with operative vaginal deliveries and Caesarean sections were 40%.

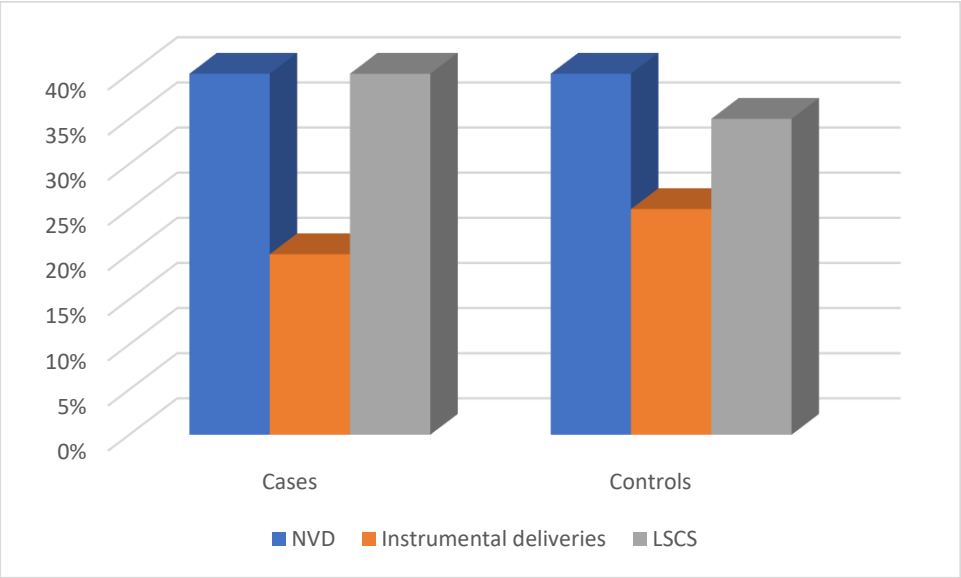


Figure 11. Mode of delivery

Figure 5 shows the frequency distribution for the mode of delivery. For cases 40% (n=8) was normal vaginal delivery, instrumental delivery 20% (n=4) while that by LSCS was 40% (n=8). For controls normal vaginal delivery accounted for 40% (n=8), Instrumental Delivery accounted for 25% (n=5) while LSCS was 35% (n=7).

6. Gestational Age at delivery

The average gestational age at delivery was 38 weeks with 90% delivering at term and 7% delivered preterm.

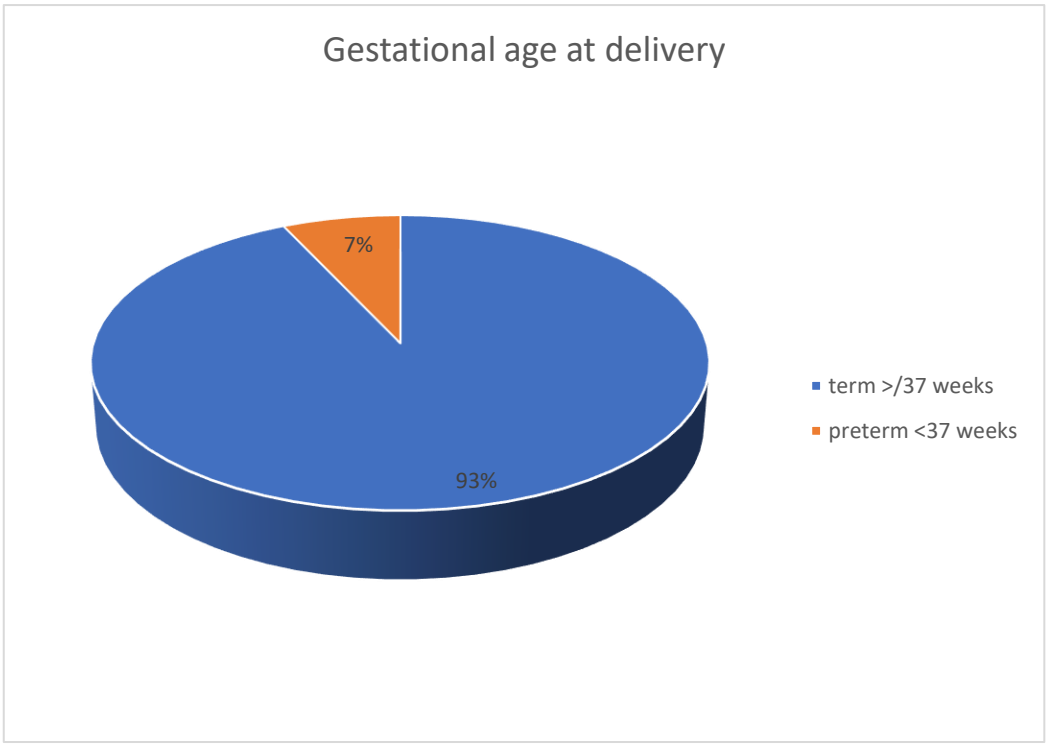


Figure 12. Gestational age at delivery

6. Birth weight

Overall the birth weight varies from 1.8 to 4.14 kg with a mean of 2.9 kg.

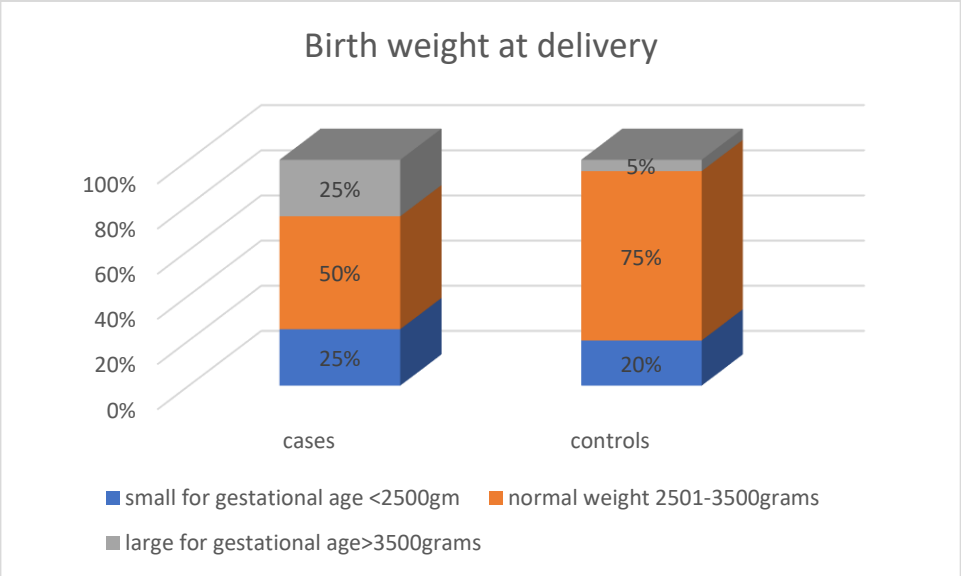


Figure 13. Birth weight distribution

Figure 7 shows the categorisation of babies as per birth weight. Categories were Low birth weight (LBW) < 2500 grams, normal weight between 2501-3500 grams, Large for gestational age (LGA) as > 3500 grams. Amongst cases 25% were < 2500 grams, 50% were in 2501-3499 grams and 25% were in > 3500 gram category while for controls 20% were LBW, 75% normal weight and 5% was LGA.

Birth weight in kg		
	cases	controls
Mean ± SD	3.07±.553	2.89±.464
Range	2.26-4.14	1.8-3.6

7. Gender of baby

There was nearly equal distribution of boys and girls among the babies delivered with boys comprising of 55 % and girls 45%. There was equal distribution of boys and girl among cases and control with each group having 11 boys and 9 girls.

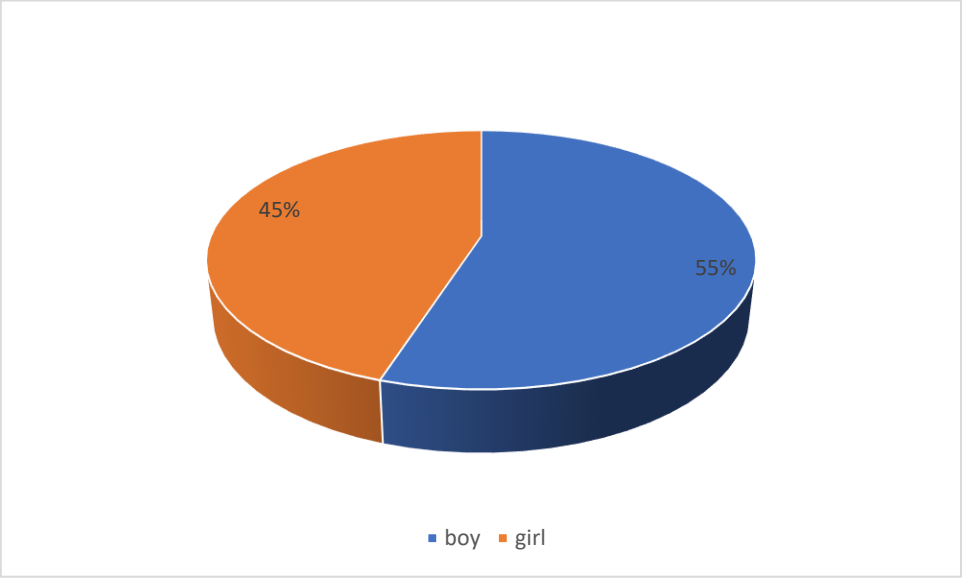


Figure14. Sex of the baby

8. Maternal risk factors

GDM

Among the women who developed hypertensive disorders of pregnancy, Gestational diabetes mellitus was seen in 70% (n=14) of patients while in the matched controls only 30% of pregnancies were complicated by GDM.

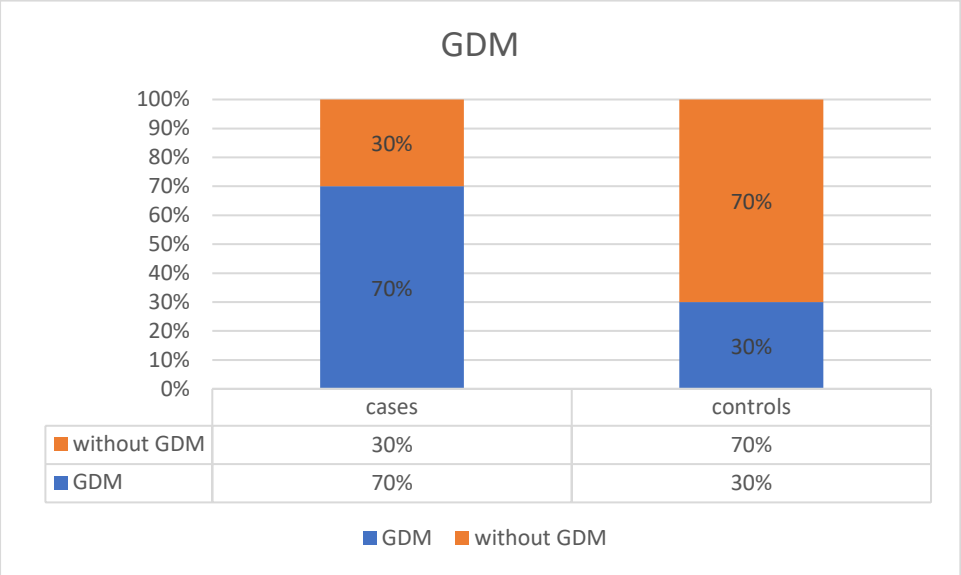


Figure 15. GDM

Hypothyroidism

There were no cases of hypothyroidism among the cases while 20% controls had hypothyroidism(n=4)

Anemia

Among the cases 30% women had anemia while only 20% had anemia among the controls. All patients had mild anemia, with no moderate or severe anemia.

9. Lipid profile of cases

First trimester Total cholesterol levels were in the dyslipidemic range of >160mg/dl in 95% cases (n=19) with only 5% (n=1) in the normal range. 65% (n=13) of cases and had Triglyceride levels >150 mg/dl and 35% (n=5) were normal. HDL cholesterol was less than 50mg/dl in 70% (n=14) with only 30% normal. In LDL cholesterol, the trend showed a difference with only 35 % (n=7) being in the dyslipidemic range and 65% in normal range.

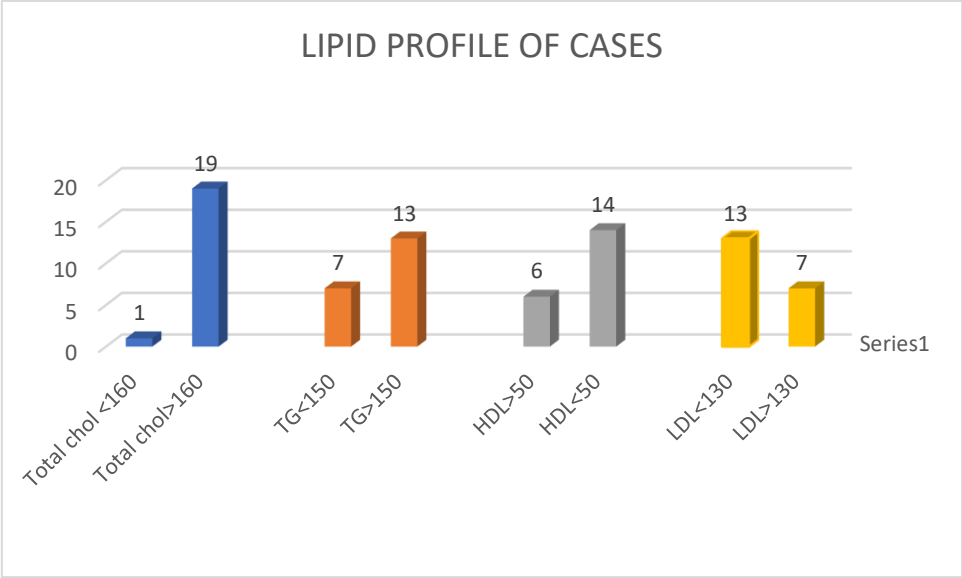


Figure 16. shows the pattern of lipid profiles in cases

10. Lipid profile of controls

For controls, the total cholesterol and triglycerides was high for 60% (n=12) and 55% (n=11) and was in the normal range for 40% and 45% respectively. HDL cholesterol, was normal in only 15% with 85% being <50mg/dl. LDL cholesterol, findings were similar to that of cases with 35% being in the dyslipidemic range and 65% normal.

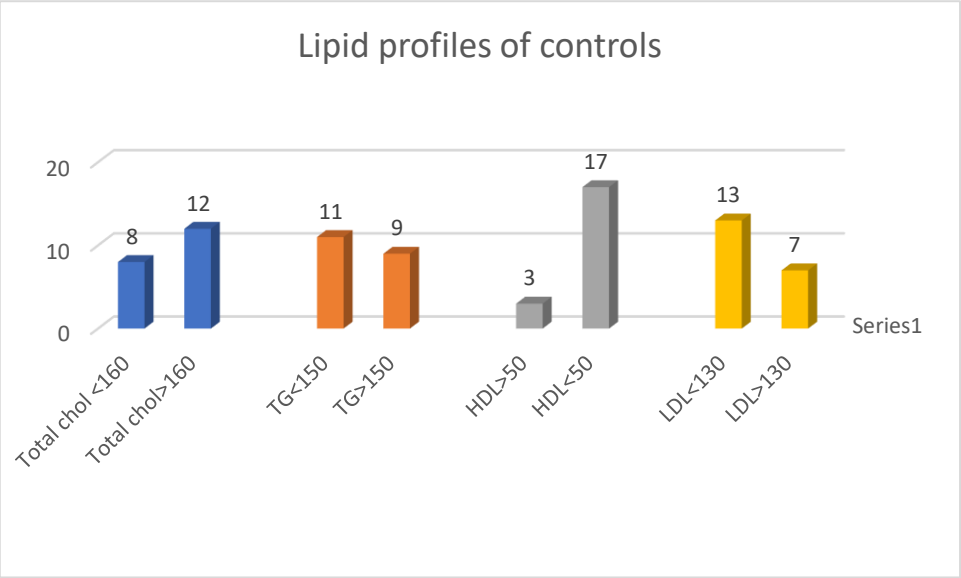


Figure 17. Lipid profiles in controls

11.Total Cholesterol

The total cholesterol levels for both cases and controls were in the dyslipidemic range with 95% of cases and 60% of controls having high levels of total cholesterol. (*p* value-0.051)

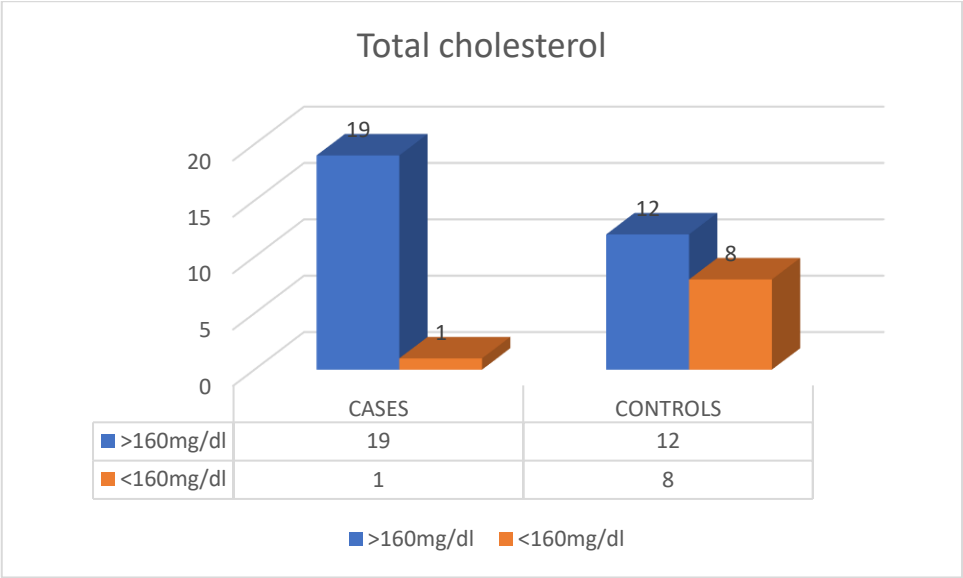


Figure 18. Total cholesterol for cases & controls

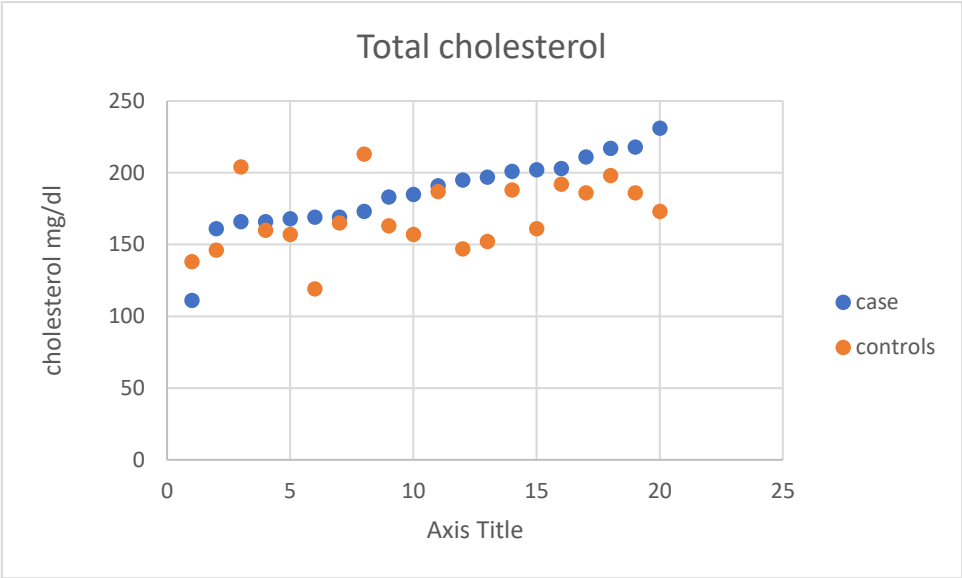


Figure.19. Scatter diagram of Total Cholesterol (Cases & controls)

Total cholesterol mg/dL		
	cases	Controls
Mean ± SD	185±26.914	169±24.117
Range	111-231	119-213

Mean difference	16.250
95%confidence interval of the difference	-.109 – 32.609
p value	0.051

12. Triglycerides

65% of the cases and 45% of controls had triglyceride levels > 150mg/dl with 35% and 55% of the levels being normal among cases and controls respectively. There was no significant difference between the two groups. (*p* value-0.138)

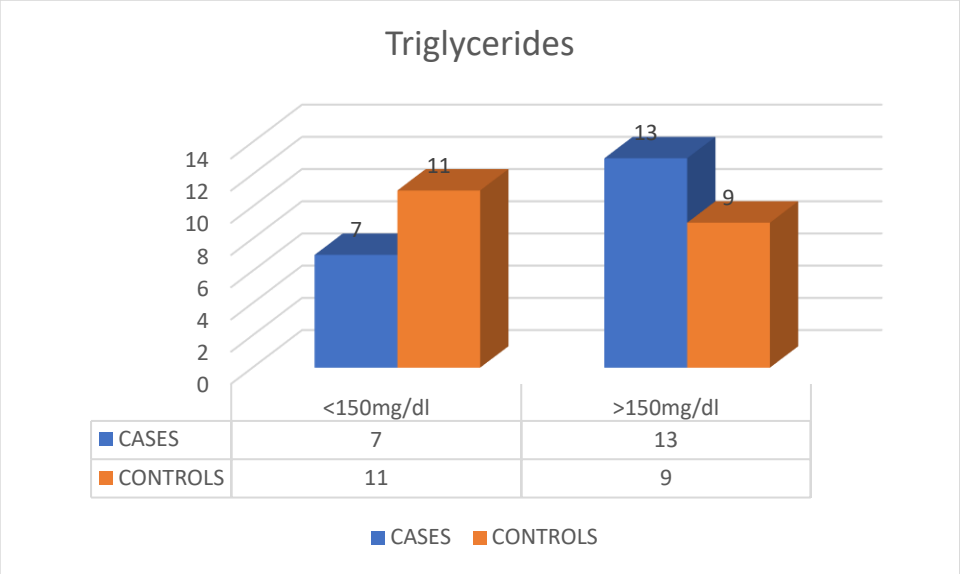


Figure 20. Triglyceride levels in cases and controls.

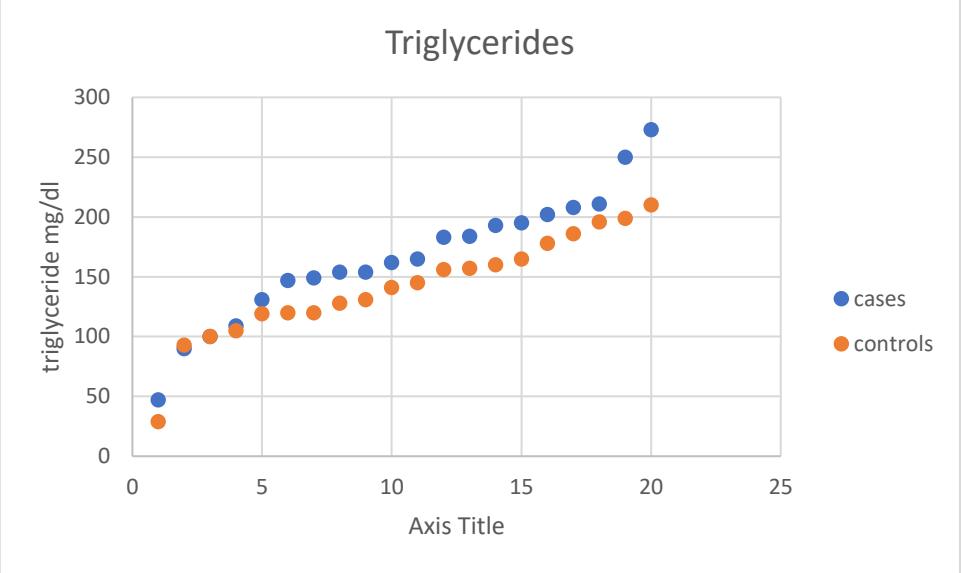


Figure 21. scatter plot of triglyceride values of all 40 cases and controls.

Triglyceride mg/dL		
	cases	Controls
Mean ± SD	165.35±54.040	141.90±43.178
Range	47-273	29-210

Mean difference	23.450
95%confidence interval of the difference	-7.862 –54.762
p value	0.138

13. HDL cholesterol

HDL cholesterol was <50mg/dl in 70% of cases and 85% of controls and was >50mg/dl in 30% of cases and 15% of controls. (*p* value- 0.249)

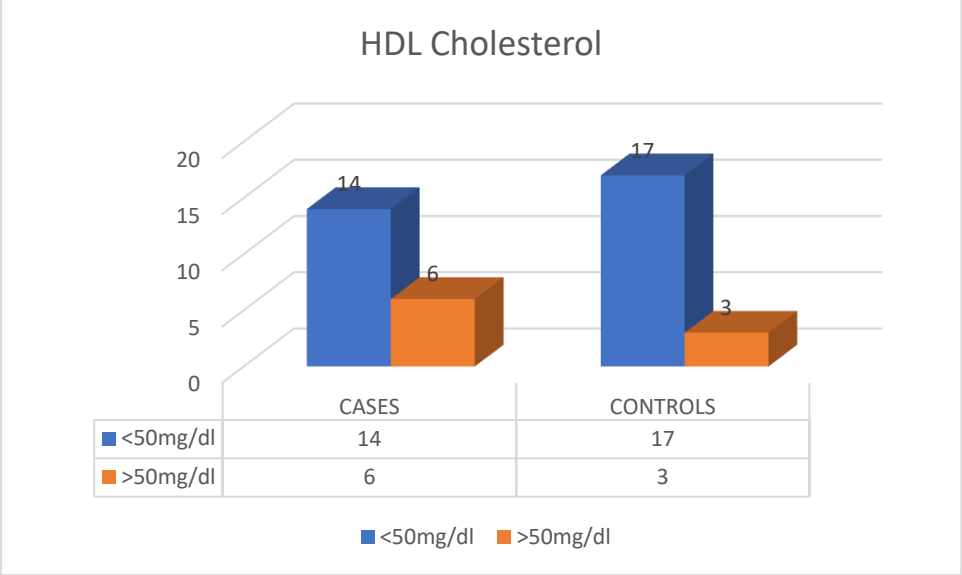


Figure 22. HDL levels

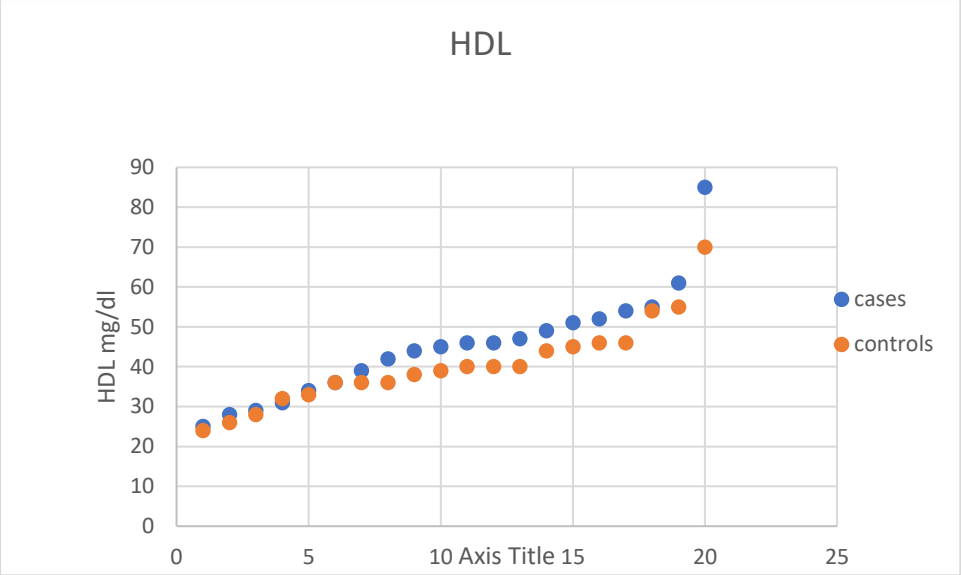


Figure 23. scatter diagram for HDL levels for all cases and control.

HDL cholesterol mg/dL		
	cases	Controls
Mean ± SD	44.95±13.636	40.40±10.743
Range	25-85	24-70

Mean difference	4.550
95%confidence interval of the difference	-3.308– 12.408
p value	0.249

14.LDL cholesterol

LDL cholesterol levels were similar in both cases and controls with 35% being in the dyslipidemic range.

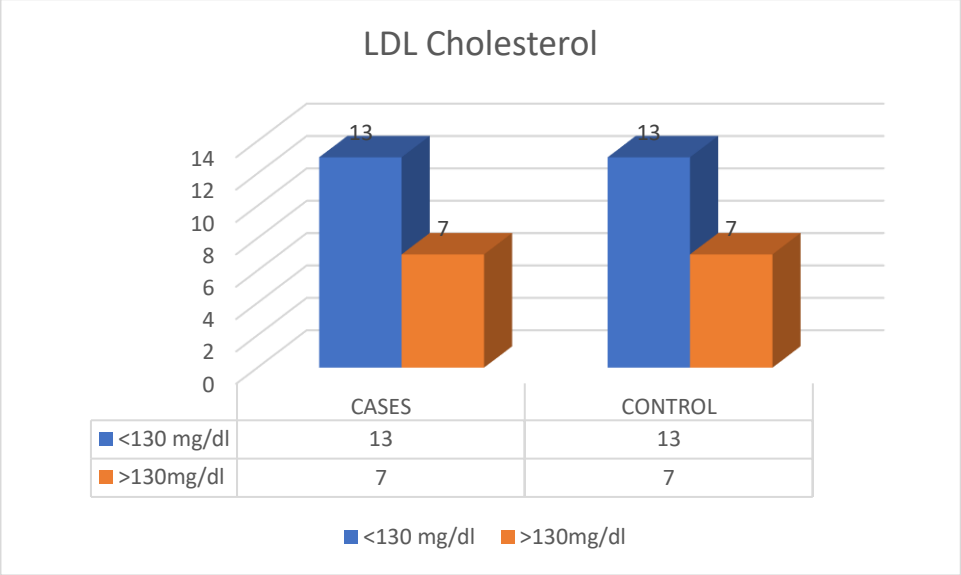


Figure 24. LDL cholesterol levels

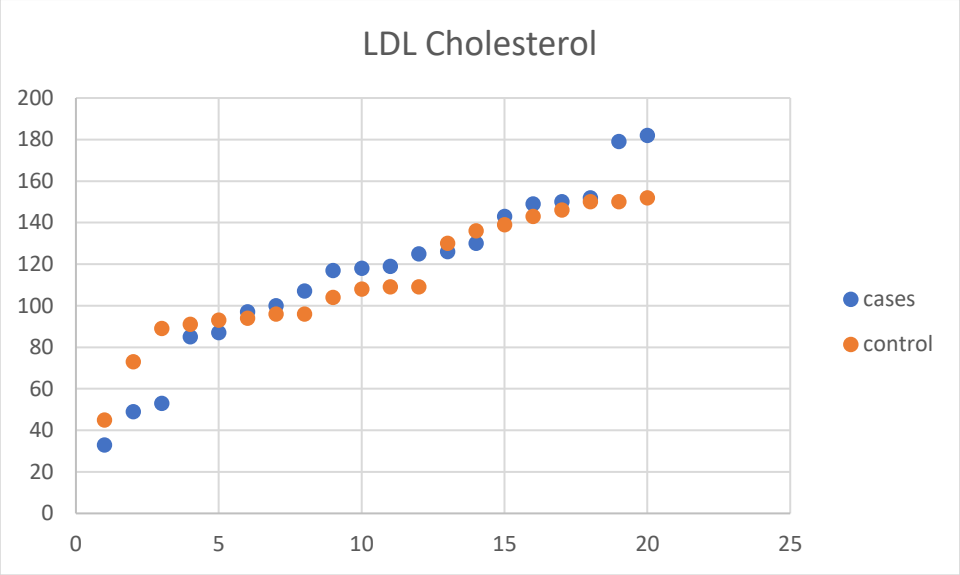


Figure 25. shows scatter diagram of all 40 cases and control.

LDL cholesterol mg/dL		
	cases	Controls
Mean ± SD	110.10±41.805	112.65±29.469
Range	33-182	45-152

Mean difference	-2.550
95%confidence interval of the difference	-25.703–20.603
p value	0.825

Gestational hypertension and preeclampsia

1.Age distribution

Though there was a statistical difference in the age on comparison between hypertensives and normotensives, no such difference was noted between gestational hypertensives and patients with preeclampsia.

Analysis of the mean age within the cases between gestational hypertension and preeclampsia showed the mean age to be 26 years for preeclampsia and 28.6 for gestational hypertension.

Maternal age (years)		
	Pre-eclampsia	Gestational hypertension
Mean ± SD	26±1.581	25±3.457
Range	24-28	25-35

Mean difference	-2.660
95%confidence interval of the difference	-6.072 - .739
p value	.117

2.Body Mass Index

Within the hypertensives, comparing the preeclampsia and gestational hypertensives, no difference was found in the BMI between the two.

3.Obstetrical score

In women with preeclampsia, Primigravidas accounted for 60% and multigravida for 40%. In women with gestational hypertension 53.3% were Primigravida and multigravida 46.7%. (p value-0.795)

	Preeclampsia	Gestational hypertension	P=.795
primigravida	60%	53.30%	
multigravida	40%	46.70%	

4.Gestational age at delivery

There was no significant statistical difference in the gestational age at delivery between the preeclampsia group (mean gestational age at delivery- 37.4 weeks) and gestational hypertension (mean gestational age at delivery-38.3 weeks.)

5.Mode of delivery

In women with Preeclampsia, 60% of women delivered normally (inclusive of operative vaginal deliveries) and 40 % by LSCS. In women with Gestational hypertensives there was a similar trend with 53.3% being delivered by Normal vaginal delivery and instrumental delivery while 46.7 % delivered by LSCS.

	Preeclampsia	Gestational hypertension	
NVD + Instrumental delivery	60%	53.30%	P = .795
LSCS	40%	46.70%	

6.Birth weight at delivery

The mean birth weight of babies born to mothers with preeclampsia was 2.69 kg while the mean birth weight of babies were born to mothers with gestational hypertension was 3.20 kg. This was found to be statiscally significant (p =0 .040)

Birth weight in Kgs		
	Pre-eclampsia	Gestational hypertension
Mean ± SD	2.69±.373	3.2±.551
Range	2.43-3.24	2.2 -4.14

Mean difference	-.515
95%confidence interval of the difference	-1.07 - .046
p value	.040

7.Antihypertensives in preeclampsia and gestational hypertension

Majority of gestational hypertensives did not require antihypertensives (73.3% did not require any antihypertensives) while all the patients with preeclampsia required anti hypertensives. Among women with gestational hypertension, only one antihypertensive was required for control of blood pressure whereas 20% of those with preeclampsia required more than one drug.

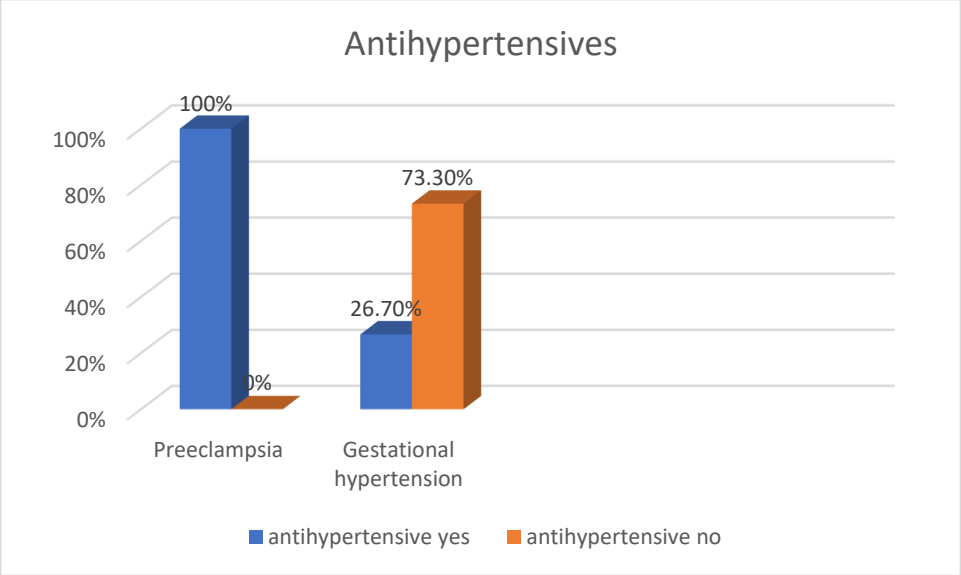


Figure26. Antihypertensive distribution

		Preeclampsia	Gestational hypertension	P=.035
Antihypertensive	yes	100%	26.7%	
	no	0%	73.3%	

8.End organ damage

60% of those with preeclampsia had evidence of end organ damage while 40 % had no end organ damage.

9.Lipid profile in cases

Figure 20 and 21 shows the lipid profile distribution of patients who developed Gestational hypertensives and preeclampsia.

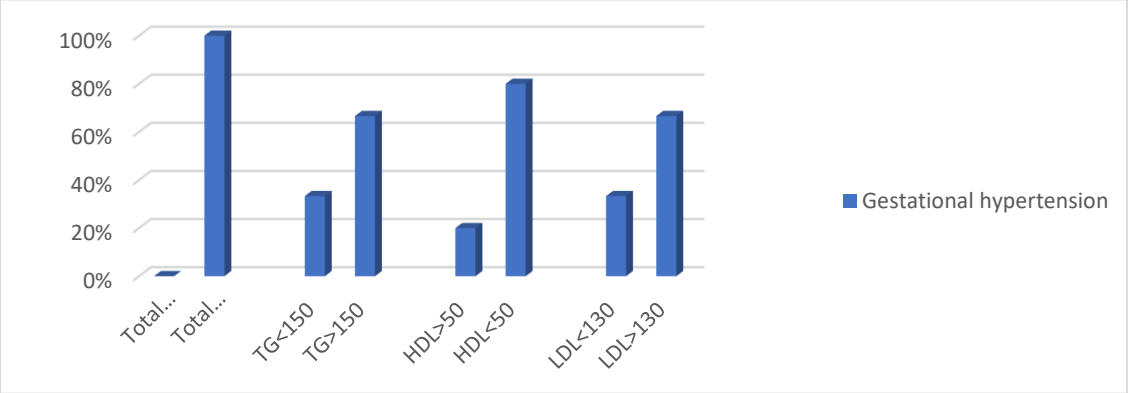


Figure 27. Lipid profile of Gestational Hypertensives

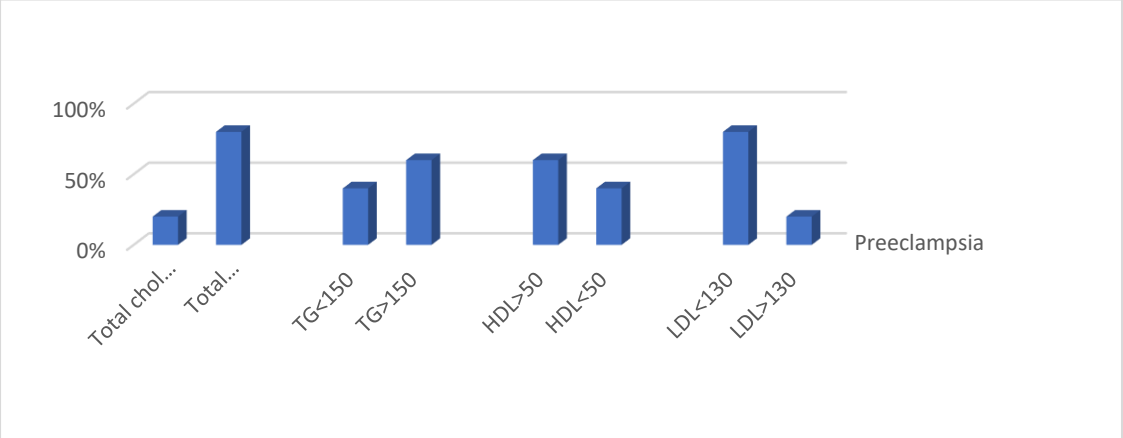


Figure 28. Lipid profile of patients with Preeclampsia

10.Total cholesterol

Among the hypertensives, 80% of patients with preeclampsia and 100% of patients with Gestational Hypertension had total cholesterol levels in the dyslipidemic range, levels being > 160mg/dl.

Total cholesterol in mg/dL		
	Pre-eclampsia	Gestational hypertension
Mean ± SD	178.60±40.87	188.27±21.92
Range	111-217	161-231

Mean difference	-9.66
95%confidence interval of the difference	-39.281- 19.948
p value	.502

11.Triglycerides

Almost similar findings were seen between the two groups with regard to triglyceride level with 60% of preeclampsia patients and 66.6% of gestational hypertensives having values greater than 150mg/dl.

Triglycerides in mg/dL		
	Pre-eclampsia	Gestational hypertension
Mean ± SD	147.20±60.14	171.40±52.65
Range	47-195	90-273

Mean difference	-24.20
95%confidence interval of the difference	-83.23- 34.83
p value	.400

12.HDL Cholesterol

Amongst the hypertensive patients, the Preeclampsia group had 40% women with HDL value <50mg/dl whereas 80% of women in the gestational hypertension group had <50 mg/dl.

HDL in mg/dL		
	Pre-eclampsia	Gestational hypertension
Mean ± SD	49.80±9.39	43.33±14.69
Range	36-61	25-85

Mean difference	6.646
95% confidence interval of the difference	-8.392 – 34.831
p value	0.373

13.LDL Cholesterol

20% women who developed preeclampsia and 66.6% of women with gestational hypertension had high LDL >130 mg/dl.

LDL in mg/dL		
	Pre-eclampsia	Gestational hypertension
Mean ± SD	108.400±36.108	110.67±44.698
Range	53-149	33-182

Mean difference	-2.267
95%confidence interval of the difference	-48.85 – 44.31
p value	.920

DISCUSSION

Baseline demography

Of the 222 women who were recruited, 176 women delivered in our hospital 17.5%(n=39) were lost to follow up, 6 of them had a spontaneous miscarriage at less than 20 weeks. Among these, 20 women developed hypertensive disease of pregnancy. This gave the prevalence of hypertensive disorder in our study population at 11.3 % which is similar to the rates noted in our institution. This is slightly higher than the prevalence recorded worldwide which is around 8-10 % (2). Of the women who developed hypertensive disorder, only 2.8 % developed preeclampsia which is lesser than the prevalence recorded worldwide at 4 -8%. This can be explained by the fact that all patients were booked early in pregnancy and had regular antenatal check-up at our hospital, which is a tertiary care centre and therefore had better surveillance and early intervention. The preeclampsia rates of the institution varies between 4-5%. However, most of the patients who present to us with preeclampsia are referred and their samples for lipid profiles were unavailable due to the study design.

Maternal age

The women recruited in our study were between 19 to 35 years of age. The cases and controls were BMI matched. None of the patients were beyond 35 years, as age more than 35 years is a proven risk factor for hypertensive disorder (80). The mean age of women with hypertensive disorder was 28 years and of the controls was 24.68 years.

This significant difference (p=.005) indicates that age in hypertensive disorder of pregnancy follows a progressive pattern even below 35 years. Women above 30 years of age should also be kept at for the development of hypertensive disorders. However, there was no difference with regards to age noted among women with gestational hypertension and preeclampsia.

Parity

Nulliparity is a known risk factor for developing hypertensive disorders of pregnancy (80), but in our study there was a near equal distribution of hypertensive disorder between Primigravida and multigravida. Even in the development of gestational hypertension and preeclampsia, parity was not found to be a significant risk factor.

Dietary habits

Most of the women (95%), both in cases and control were non-vegetarians. This was likely owing to the general dietary preference in our region. Few case control studies have shown a protective effect of high fruit, vegetable and folate diet against hypertensive disorder of pregnancy(111). However, in our study since there were very few who were vegetarians, no significant correlation could be made between dietary habits and development of hypertensive disorder of pregnancy.

Body Mass Index

Higher body mass index have been associated with an increased risk of hypertensive disorder of pregnancy with relative risk of 2.8 and 2.1 in those with a pre-pregnancy BMI of >30kg/m2 and BMI of >25 kg/m2 respectively. (81). As an attributable risk factor, nulliparity and obesity (BMI >30kg/m2) contributed for largest population based risk factor (80). According to the data available for Indian population from National Health Family Survey (NFHS), the percentage of married women aged 15-49 years who are overweight or obese increased from 11% in NFHS-2 to 15% in NFHS-3(88). In South India, where our hospital is located, the percentage of overweight and obese women is much higher. In the state of Kerala, the rate of obese and overweight is the highest (34%), followed by Tamil Nadu (24.4%), Andhra Pradesh (22.7%) and Karnataka (17.3%) respectively (112). Even with such high baseline prevalence of obesity in our region, our study found an even higher prevalence that is 50% among women who developed hypertensive disorder of pregnancy with BMI > 25 kg/m2. This lowers the cut off for the relative risk of developing hypertensive disorders of pregnancy for our population than earlier established BMI > 30mg/m2. This also corroborates with a large population-based cohort study done by Mbah AK et al. that showed an incremental rise in preeclampsia with obesity (94). Within the hypertensive group on comparing the preeclampsia and gestational hypertension, there was no difference in the BMI of patients who developed preeclampsia in comparison to those who remained gestational hypertensives.

Pregnancy related Outcomes

Mode of delivery

There was mild increase in the rates of LSCS in patients who developed hypertensive disorder of pregnancy than in the controls but it was not found to be statistically significant.(p value .317)

Gestational age at delivery

Immediate delivery is the definitive management for hypertensive disorders of pregnancy and hence early delivery would be expected in patients with hypertensive disorders as compared to normotensive patients. However, in our study there was no difference in the gestational age at delivery among these, with the mean gestational age of delivery for both cases and control being 38 weeks. This might be due to the fact that in our study, among the patients who developed hypertensive disorders only 20% had Preeclampsia while the rest 80% had gestational hypertension and hence were delivered at term gestation. Gestational age for delivery was also found to be similar when women with gestational hypertension and preeclampsia were compared.

Birth weight at delivery

The birth weight of neonates born to women with hypertension was found to be similar to the birth weight of neonates who were born to women who did not have

hypertension. This can be explained by the fact that the cases comprised mostly of women who developed hypertensive disorders at term and only a minority among them had preeclampsia. It has been already well established that both gestational hypertension and Preeclampsia have different pathophysiology and that factors which causes preeclampsia are also the causative factors for IUGR, Preterm labour with intact membrane, Preterm PROM, Abruptio placentae and mid trimester abortion, termed as The Great Obstetric syndrome (34). Even in Preeclampsia as proven by Milosevic-Stevanovic et al, the pathogenesis in pregnancies with and without IUGR is different(113). This was similar to findings by Jose Villar et al who found that preeclampsia and IUGR have different pathological entities. In our study, when the birth weight of neonates born to mothers with preeclampsia was compared with birth weight of neonates born to mothers with gestational hypertension it was found that the mean weights were 2.69±.337 kg and 3.2±.551 kgs respectively and these were statistically significant (p=.040). This finding was similar to Srinivas et al who found that preeclampsia is independently associated with IUGR and that there was no similar association between chronic hypertension and IUGR(114).

Dyslipidemia and hypertensive disorder of pregnancy

Dyslipidemia are disorders of lipoprotein metabolism which includes both lipoprotein overproduction and deficiency. They are marked by one or more of the following which include elevated Total cholesterol >160mg/dl, triglyceride >150mg/dl, LDL >130mg/dl and HDL <50mg/dl. With the above criteria, 90% women who developed

hypertensive disorder of pregnancy had dyslipidemia in their first trimester with Total cholesterol being in dyslipidemic range.

Total Cholesterol

Various studies have suggested a positive correlation between maternal dyslipidemia and development of preeclampsia with hypertriglyceridemia and hypercholesterolemia being the major risk factors for the same. In a prospective cohort of study involving 393 pregnant women, Wladimiroff et al reported that women with total cholesterol concentration > 6 mmol/L(>233mg/dl), compared with those whose concentration were <5mmmol/L(<194mg/dl) experienced five-fold increased risk of preeclampsia (95%CI 1.2to 22.5) after accounting for confounding by maternal BMI and gestational age(10). Enquobarhie et al noted a 3.60 fold increase in risk of preeclampsia among women with total cholesterol >205 mg/dl (upper tertile), as compared with women whose total cholesterol concentration was <172mg/dl(lower tertile) after adjusting for confounders(OR=3.60, 95%CI 1.23 to 10.51)(13) In a prospective cohort, Nabih et al found significantly high cholesterol level in women who developed preeclampsia (p<.0001) and even higher in severe Preeclampsia than in mild preeclampsia(p=.009) with a cut-off point of 231mg/dl, below which the likelihood of Preeclampsia occurring was very less with a negative predictive value of 96%(115).

In our study we found a similar correlation between early trimester hypercholesterolemia and development of hypertensive disorder of pregnancy. The mean total cholesterol for women with hypertensive disorder was 185±26.914 and for

their BMI matched control was 169±24.117 with a statistically significant correlation (p=.05, 95% CI.-.109 to 32.609). But when total cholesterol levels were compared between the gestational hypertension and preeclampsia no significant correlation was observed.

Triglycerides

Various prospective cohort and case control studies have established the strong correlation of early trimester hypertriglyceridemia with hypertensive disorders. Lorentzen et al found that at 16-18 weeks the mean triglyceride concentration of 19 women who later developed preeclampsia were 1.3±0.5mmol/L (50.4±19.4 mg/dl) as compared to matched control subjects with 0.9±0.3mmmol/L (34.91±11.64mg/dl) who had normotensive pregnancies(p<.01)(8) Ware-Jauregui et al in a case study in Peruvian women reported that triglyceride level concentration > 284mg/dl have a five-fold increased risk of developing preeclampsia as compared to women whose concentration was <189.0 mg/dl(107). Enquoabahrie et al noted a positive correlation with risk of preeclampsia, Women in highest tertile for triglycerides experienced a 4.15 fold increased risk of preeclampsia as compared with those women in lowest tertile(adjusted OR=4.15, 95% CI1.50 to 11.49). The risk of preeclampsia increased with successive higher tertiles of plasma triglycerides (adjusted OR1.00,2.25 and 4.15 with lowest tertile as referent, P=.005)(13). Few studies showed correlation between severity of preeclampsia and hypertriglyceridemia like Nabih et al found where found that there is a significant altered triglyceridemia level when severe and mild preeclampsia were compared (p=.016). Gratacos et al noted in their study that

triglyceridemia is significantly elevated in severe gestational hypertension, mild and severe preeclampsia but there was no elevation in cases with mild gestational hypertension and chronic hypertension(116).

On the contrary, Baker et al found that women with more severe form of Preeclampsia had triglyceride levels which were similar to normotensive control subjects but in these studies the samples were collected in mid trimester, hence these cannot be a representative of first trimester cholesterol levels(117).

In our study we found that mean Triglyceride levels were 165.35±54.040mg/dl while the controls had 141.90±43.178mg/dl, this finding was similar to previous studies, although in our study we did not find a statistically significant elevated triglyceridemia(p=.138) among women who developed hypertensive disorders of pregnancy.

When women who had gestational hypertension was compared with women who developed preeclampsia there was no statistical correlation with triglyceride levels (p=.400).

HDL Cholesterol

The role of HDL cholesterol in hypertensive disorder is not very clear. A study from sub Saharan region William et al reported that there is an inverse association between risk of developing preeclampsia and HDL cholesterol (81) Similarly, low preconception levels of HDL-c and high levels of triglycerides were found to be independently associated with an increased risk for preeclampsia and/or gestational

diabetes mellitus, while the highest rates of this composite outcome were observed in a group with both high triglycerides and low HDL-c(108)

While on the other hand Lima VJ et al. found that there was no significant correlation between the HDL levels and preeclampsia(118). Demirci et al. also did not find any significant correlation between HDL levels in early pregnancy and risk of developing preeclampsia(119).

In our study we did not find any significant difference in HDL levels in cases and controls which was 44.95±13.636 and 40.40±10.743 respectively with mean difference of 4.55 mg/dl p=.249. Similarly, no significant difference was found when HDL levels of women who had gestational hypertension was compared with women who had preeclampsia(p=.373).

LDL Cholesterol

LDL cholesterol has not been found to be definite predictors for developing while some study such as Enquobahrie et al. reported that in pregnant women who subsequently developed preeclampsia had high concentration of LDL cholesterol in comparison to women who remained normotensive(13). On the other hand study by Nabih et al. showed insignificant correlation between elevated LDL levels and development of preeclampsia, they also found that there was no significant elevation in LDL levels when severe and mild preeclampsia were compared(115).

In our study we did not find any difference in LDL levels between patients who developed hypertensive disorders of pregnancy and their normotensive counterparts

(cases 110±41.805 and controls 112.65±29.469, mean difference -2.550, p=.825). When LDL levels were compared within women with gestational hypertension and preeclampsia, the results were similar with no significant correlation between the two (p=.920), hence our study conforms with findings of earlier studies.

CONCLUSION

- Maternal age has a linear relation with the risk of developing hypertensive disorders of pregnancy even below 35 years.

- Patients who are above the age of 30 years should have increased surveillance as they are at risk of developing hypertensive disorders of pregnancy.

- Birth weight of the babies born to mothers with preeclampsia were significantly lower than those born to mothers with gestational hypertension

- Pre-pregnancy BMI of the mother significantly increases the risk of developing hypertensive disorders of pregnancy. In our population, BMI of > 25kg/m2 was noted to have a higher risk of developing hypertensive disorders in pregnancy.

- First trimester hypercholesterolemia correlates significantly with the risk of developing hypertensive disorders in the latter part of pregnancy. However, the levels did not correlate with the severity of hypertensive disorders as no difference was noted in the level of hypercholesterolemia when gestational hypertension was compared with preeclampsia.

- There was moderate correlation between first trimester hypertriglyceridemia and hypertensive disorder of pregnancy but there was no such association found when triglyceride levels were compared with Gestational hypertension and preeclampsia.

- First trimester HDL and LDL levels did not show any significant correlation with hypertensive disorder of pregnancy.

LIMITATIONS

- Even though the first trimester samples were collected from patients after the assurance that they will deliver in our institution, around 17.5% were lost to follow up.
- Samples of 2 patients who developed hypertensive disorder (1 with severe PE and 1 gestational HT) could not be analysed as it had lysed.

- Due to the small sample size, the lipid profiles of non-severe and severe preeclampsia could not be compared.
- Detailed dietary history could not be elicited due to lack of time.

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Appendix 1

PROFORMA

IRB NO 10851

Name

Hospital No

Date of visit

Age: Years

LMP: / / (dd/mm/yyyy)

EDD: / / (dd/mm/yyyy)

GA: weeks days

Weight: kg Height: cm BMI: kg/m2

Obstetrical score:

Diet: Vegetarian/ Non- vegetarian

To be filled at time of delivery

GA at delivery : weeks days

Mode of delivery:

Sex of baby: Boy/girl

Birth weight of baby:

Neonatal complication : Yes/ No

BP

Normal

140-159/90-109 mmHg

>160/110 mmHg

Urine protein Dipstick ___+

End organ damage : Present/Absent

Antihypertensive: Yes/No

No. of antihypertensives:

Lipid profile: Total cholesterol/ HDL/ LDL/ TG

Appendix-2 Data

sno	Name	Hospital No.	Age	GA at recruitment	BMI	obstetrical score	diet	Mat. Com	GA at delivery	Birth weight	Sex of baby	nursery admission	mode of delivery	Systolic BP	Diastolic BP	Urine protein	end organ damage	antihypertensive	no. anti hypertensive	T.Chol	LDL	HDL	TG
1	BHAGYA	077321 H	28	13	28	1	1	GDM-Diet,anemia	38	3.34	1	0	3	160	100	Nil	0	1	1	201	152	28	184
2	VISHNUPRIYA	049409 H	25	12	27	1	1	GDM-Insulin	37	2.26	2	0	3	140	90	Nil	0	1	1	183	119	44	162
3	JAYALAKSHMI	923716 B	24	10	23	2	1	anemia	36	2.89	1	0	1	150	90	1+	0	1	1	173	97	46	195
4	REKHA G	452827 F	36	10	27	2	1	anemia	39	3.17	2	0	1	140	90	Nil	0	1	1	218	179	39	90
5	LILLY CHITRA	001974 B	26	9	17	1	1	GDM-Diet	37	2.48	2	1	3	140	100	nil	0	1	1	169	49	45	109
6	MONICA	644436 B	26	12	25	1	1	anemia	37	2.59	1	1	2	150	100	2+	1	1	1	217	149	61	154
7	SUGANYA A	727727 F	29	11	23	2	1	GDM-Diet	40	3.39	1	0	1	140	90	Nil	0	0	nil	203	126	46	208
8	SINDHUJA	078782 H	27	12	29	1	2	nil	37	2.4	1	1	3	150	90	2+	0	1	1	197	125	36	193
9	ARUNA DEVI	058849 H	30	16	31	1	1	GDM-Diet	37	2.4	2	0	1	140	90	Nil	0	0	nil	211	130	55	183
10	CHANDU SREE	193204 G	29	11	24	2	1	GDM-OHA	38	3.64	1	0	3	140	90	Nil	0	0	nil	191	143	31	154
11	GAYATHRI	348641 F	26	9	24	2	1	nil	40	3.9	1	0	1	140	90	nil	0	0	nil	202	150	51	131
12	NANDHINI S	987432 A	26	12	28	1	1	GDM-Insulin	38	2.82	2	0	2	140	90	nil	0	0	nil	168	117	34	165
13	SHARMILA R	123587 H	25	12	23	1	1	GDM-Diet	37	2.91	2	0	1	140	100	nil	0	0	nil	166	107	47	149
14	DHANA RANI P N	672312 F	27	14	21	2	1	GDM-OHA	39	4.14	1	0	2	140	90	nil	0	0	nil	231	182	42	100
15	KUBRA KOWAIN	246215 G	28	12	29	2	1	anemia	38	2.34	2	0	1	180	120	4+	1	0	3	195	118	54	147
16	ATEEQA	018347 H	25	13	19	1	1	GDM-Diet	39	3.24	1	0	3	160	110	3+	1	1	nil	111	53	52	47
17	ANUPRIYA	613366 D	30	14	26	2	1	GDM-Diet	38	3.12	2	0	3	140	90	nil	0	0	nil	169	100	49	202
18	KALAIVANI DANAPAL	122260 H	36	11	31	1	1	GDM-Diet	39	3.3	2	0	3	140	90	nil	0	0	nil	161	87	29	211
19	GOVARTHINI	130225 H	27	11	24	1	1	GDM-Diet	38	3.6	1	0	1	140	90	nil	0	0	nil	166	33	85	273
20	THILAGAVATHI	773889 F	30	12	17	2	1	anemia	40	3.64	1	0	2	140	90	nil	0	0	nil	185	85	25	250

primi-1 non veg-1 nvd-1 end organ damage present-1 Boy-1

multi-2 veg-2 insrtrumental-2 antihypertensive present 1 Girl -2

lscs-3

sno	Name	Hospital No.	Age	GA at recruitment	BMI	obstetrical score	diet	Mat. Com	GA at delivery	Birth weight	Sex of baby	nursery admission	mode of delivery	Systolic BP	Diastolic BP	Urine protein	end organ damage	antihypertensive	no. anti hypertensive	T.Chol	LDL	HDL	TG
1	MANJULA	023685 B	25	9	28	1	1	hypothyroidism	39	2.8	1	0	3							188	146	54	93
2	PRIYA S	098819 H	26	14	27	2	1	GDM-OHA	38	2.9	2	0	3							163	94	32	196
3	PRIYA SRINIVASAN	159890 G	32	16	23	2	1	hypothyroidism	39	3.1	1	0	1							213	152	36	210
4	INDHUMATHI	089270 H	21	13	28	2	1	nil	36	2.4	1	0	1							186	136	40	145
5	ABHINAYA	055224 H	23	6	17	1	1	anemia	39	3.3	1	0	2							119	45	70	119
6	PRACHITA DEVI	736235 C	23	12	25	1	1	hypothyroidism	39	3.1	2	0	1							198	130	45	165
7	SANDHIYA	446197 G	26	15	23	2	1	nil	37	2.4	2	0	3							192	109	40	156
8	VAISHNAVI	833831 F	22	13	29	1	1	GDM-OHA,hypothyroidism	39	2.6	1	0	1							152	96	44	141
9	MOHANA LAKSHMI	111645 H	27	14	30	1	1	cholestasis	30	3.6	1	0	2							186	139	40	157
10	JAYA BHARTHI	301291 C	33	11	25	2	1	anemia	37	2.8	1	0	3							187	96	36	29
11	VIJAYALAKSHMI	244973 G	26	9	24	2	1	PPROM	39	3.37	2	0	1							161	108	55	100
12	MUBEENA BANU	102544 H	19	12	28	1	1	GDM-Diet	38	2.5	2	0	2							157	109	38	120
13	ABIRAMI	703552 A	23	15	23	1	1	GDM-Diet	39	3.2	1	0	1							204	150	36	178
14	SELVI ISHWARIYA	600015 G	24	10	21	2	1	GDM-Diet	39	2.2	2	0	2							173	143	24	128
15	GAYATHRI	107942 H	27	13	29	1	1	nil	39	3.4	2	0	2							147	73	46	160
16	GAYATHRI	084192 H	19	9	19	1	1	nil	39	2.8	2	0	1							138	91	33	120
17	MADHUMATI	754363 B	26	10	26	2	1	nil	39	3	1	0	3							165	93	46	131
18	DHARANI	841895 f	28	9	30	2	2	GDM-OHA	37	1.8	2	1	3							146	89	28	186
19	SARANYA R	089582 H	23	13	24	2	1	anemia	40	3.3	1	0	3							160	104	26	199
20	JAYALAKSHMI	029005 H	20	14	17	1	1	GDM-Diet,anemia	39	3.3	1	0	1							157	150	39	105

primi-1 non veg-1 nvd-1 end organ damage present-1 Boy-1

multi-2 veg-2 insrtrumental-2 antihypertensive present 1 Girl -2

lscs-3

URKUND

Urkund Analysis Result

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